HOUSE OF LORDS SESSION 1992–93

SELECT COMMITTEE ON SCIENCE AND TECHNOLOGY

REGULATION OF THE UK BIOTECHNOLOGY INDUSTRY AND GLOBAL COMPETITIVENESS

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UP TO 30 APRIL 1993

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INVITATION TO SUBMIT WRITTEN EVIDENCE (UNITED KINGDOM)

SELECT COMMITTEE ON SCIENCE AND TECHNOLOGY

SUB-COMMITTEE II—REGULATION OF THE UK BIOTECHNOLOGY INDUSTRY AND GLOBAL COMPETITIVENESS

The House of Lords Select Committee on Science and Technology have appointed a Sub-Committee, under the chairmanship of Lord Howie of Troon, to enquire into "Regulation of the UK Biotechnology Industry and Global Competitiveness".

The Sub-Committee invite you to submit written evidence to them on any matters relevant to their terms of reference and in particular on the question enclosed with this letter. It may be that not all the questions will be relevant to your concerns, in which case you should be selective.

Evidence should be submitted to me, the Clerk of Sub-Committee II (Regulation of the UK Biotechnology Industry and Global Competitiveness), Select Committee on Science and Technology, House of Lords, London SW1A 0PW. Evidence must be clearly printed and take the form of an original copy. Pre-published documents and documents prepared for other purposes will not normally be received as evidence. It would assist the Sub-Committee if evidence were prefaced with an executive summary or precis.

On the basis of written evidence received the Committee will invite some witnesses to give oral evidence.

If you have any queries arising out of this letter please let me know.

R H WALTERS

Clerk of Sub-Committee II

SELECT COMMITTEE ON SCIENCE AND TECHNOLOGY

SUB-COMMITTEE II—REGULATION OF THE UK BIOTECHNOLOGY INDUSTRY AND GLOBAL COMPETITIVENESS

Questions on which evidence is invited

1. What is your interest in biotechnology?

2. How and why is biotechnology important to UK industry?

3. What future prospects and opportunities does the technology offer?

4. Which developments in biotechnology raise issues of safety and how should they be addressed?

5. Should biotechnology be regulated by an industry specific regime?

6. From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?

7. Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?

8. How do current regulations compare with those of other competitor countries
— in Europe
— in the Far East
— the USA?

9. What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards
(1) research
(2) product development
(3) investment
(4) location
(5) sales and marketing?

10. Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?

11. How best can issues of public acceptance be addressed?

12. What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?

INVITATION TO SUBMIT WRITTEN EVIDENCE (FOREIGN)

SELECT COMMITTEE ON SCIENCE AND TECHNOLOGY

SUB-COMMITTEE II—REGULATION OF THE UK BIOTECHNOLOGY INDUSTRY AND GLOBAL COMPETITIVENESS

The House of Lords Select Committee on Science and Technology have appointed a Sub-Committee to consider "Regulation of the UK Biotechnology Industry and Global Competitiveness". The Sub-Committee was set up following representations that UK industry was likely to be placed at a competitive disadvantage by this country's present regulatory regime. The enquiry is expected to last until July.

As part of their enquiry, the Sub-Committee are anxious to discover what regulatory arrangements are in place in competitor countries and I should be grateful if you could provide answers to the following questions:

1. How important does your Government perceive biotechnology to be?
2. Which developments in biotechnology are thought to raise safety issues?
3. In your country, is biotechnology regulated by a specific regulatory regime?
4. Do regulations distinguish between contained use and general release (for experiment or marketing)?
5. Is regulation in your country "horizontal" (where a product is judged through the process by which it is derived) or "vertical" (where a product is judged by its characteristics)? Which is preferred by your Government?
6. Is biotechnology publicly accepted in your country?
7. Has your Government implemented EC Commission Directives 90/219/EEC and 90/220/EEC. If so, how? If not, when do you expect to do so?

I should be grateful if you could provide this information by 16 April 1993.

If you have any queries please let me know.

R. H. WALTERS
Clerk of Sub-Committee II

EVIDENCE ALREADY PUBLISHED

Witnesses	*Date*	*HL Paper*	*ISBN*
Health and Safety Executive/ Department of the Environment	11.3.93	80-i	0 10 483293 2
Department of Trade and Industry/ Ministry of Agriculture, Fisheries and Food	25.3.93	80-ii	0 10 483393 9
Zeneca/ Glaxo	1.4.93	80-iii	0 10 483693 8

WRITTEN EVIDENCE

Evidence from the Agricultural and Food Research Council

SUMMARY

AFRC has major research programmes underpinning biotechnology. Substantial opportunities are coming forward for British industry. There will be concern about safety, but risk should be objectively assessed and not be overstated. Vertical, product-based, regulation has advantages. The present UK regime is onerous and, if not handled carefully, could lead to loss of research and industrial opportunity to other countries. Public perception is a key factor—with scientists themselves having a major role to play in openly explaining the subject to the public.

1. *What is your interest in biotechnology?*

The AFRC's misssion is to advance scientific knowledge for agriculture, food and other biologically-based industries and for sustainable use of land and biological resources. The Council's research provides scientific options for new technology, new crops and improved efficiency for farming; improved processes for food, fibres and other biological products; understanding of food safety and quality, and improving environmental standards. The AFRC is dedicated to benefiting the nation's economic and industrial performance and to the public interest.

To fulfil this mission the Council supports an extensive programme of research in institutes and universities covering many aspects of biological, engineering and related sciences. This comprises work on molecules and macromolecules and genetic resources through studies of organism development to biological systems and their interaction with the environment. The programme covers animals, plants, food systems and microorganisms.

Definitions of "biotechnology" vary; it is generally taken to mean the industrial application of biological organisms, systems and processes but the science underpinning such developments must also be taken into account. A significant element of AFRC's work is therefore relevant, and includes a major programme on genetic modification. "Biotechnology" is wider than genetic modification alone, but the comments below concentrate on this particular area of scientific, industrial and public interest.

2. *How and why is biotechnology important to UK industry?*

3. *What future prospects and opportunities does the technology offer?*

The past two or three decades have seen a revolution in the biological and related sciences, and this is continuing. New knowledge of molecular structure and genetics, combined with fundamental advances at the cellular level, is being used to understand and regulate development of plants, animals and micro-organisms. These advances are dramatically changing the way scientists can grasp the structure and function of biological systems, with unprecedented possibilities for understanding the critical biological factors of the global ecosystem.

There are extensive opportunities arising from the strength of the agricultural, food pharmaceuticals and biotechnology companies underpinned by this internationally competitive science base. Options are being provided for wealth creation through development of novel products and processes, but also for more environmentally sensitive product, for better health care and for safer and more nutritious food. In a wider context, biotechnology offers tremendous opportunities for alleviating problems in the developing countries of food shortage, environmental pollution and disease.

The scientific and technological options emerging from AFRC's area of interest have recently been identified in the widely circulated publication 'Biotechnology, Agriculture and Food' (OECD, Paris 1992), which four AFRC Directors of Research played a key part in producing. Major options include:

- Plants; diagnostics for quality control, new genes for crops, improved plant breeding and production.
- Animals including fish; improved animal health and welfare, diagnostics, improved efficiency of reproduction, growth and lactation, new sources of feed and better nutrition.
- Food; safety contamination tests, new food enzymes, food flavours, biopreservation without the use of synthetic chemical preservatives, novel foods, plant cell culture.
- Non-food use of crops; fuels, oils, starches and other polysaccharides turned into industrial products, fibres, enchancement of plant and animal products.
- Novel industrial products from plants and animals; chemicals, new pharmaceuticals, antibiotics and vaccines.
- Waste treatment; residues, wastes and effluents from agriculture and food production can be treated, sometimes leading to useful by-products.

Together these comprise a very wide range of developments, providing scope for significant advance in major segments of UK industry. The rate of take-up must not be over-estimated (as may have happened in the past) but there will certainly be significant impact on the biosciences industry by the turn of the century and a major impact in subsequent years.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed*

As in many areas of endeavour, some advances in biotechnology can raise issues of safety, but it should not necessarily be assumed that new developments in biotechnology pose special risks. This is particularly so in relation to genetic modification of organisms—the area of most public interest, and often perceived to be inherently unsafe. Any risks involved need to be assessed objectively, and regulation formulated accordingly.

The issue of safety—which is taken here to mean both human health and safety and also environmental protection—needs to be addressed in two ways. Firstly there must be a continuing programme of research to provide an objective basis on which risk can be properly quantified. Along with other bodies, the AFRC is undertaking research on the effect of the release of modified organisms into the environment. The PROSAMO project (Planned Release of Selected and Modified Organisms) funded by DTI, AFRC and industrial companies has been studying the ability of genetically modified agricultural crops to breed with wild relatives, and developing new methods of microbial detection to study the fate of introduced organisms into the natural environment. Research is continuing in these and related areas. AFRC is particularly well placed to bring together the new recombinant technologies with the expertise required for ecological assessment—including taxonomy, morphology, ecology and population biology.

Secondly, the legislation and safety procedures in place must provide a regime of balanced assessment and regulation. Such regulation should be derived from an objective assessment of the risks involved, drawn from the science base, but be sensitive also to the needs of industry and to the concern of the public. There are particular considerations in relation to genetically modified products in the food chain, and scientific assessment of short and long term food safety must contribute to discussions of food regulation.

5. *Should biotechnology be regulated by an industry specific regime?*

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which is it derived) better than vertical regulation (where a product is judged by its characteristics)?*

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

Regulations that are primarily based on the process by which a product is dervied are unsatisfactory. This may be necessary at the current stage, where there are only a small number of products to consider and when immediate public concern is with novel processes such as genetic modification. With greater experience and knowledge product based "vertical" regulation is preferable. Similar processes applied to different products might have unrelated outcomes; and the range of products is very wide, requiring different assessments. In any event, product related regulations will include consideration of those characteristics which result from the mode of production; for example, if a product is made using recombinant DNA techniques, its novel characteristics will include changes brought about by the introduced DNA and the new genes expressed.

AFRC therefore favours more emphasis on a vertical, product-based, regulation regime, focussed on assessment of the product characteristics, but recognises continuing public interest in mode of production. As now, advice on elements of the process such as release of genetically modified organisms into the environment would continue to be given by the Advisory Committee on Release to the Environment and the Advisory Committee on Genetic Modification. The Advisory Committee on Novel Foods and Processes and the Food Advisory Committee should continue to advise Government on the particular considerations related to food safety and food labelling.

The extent to which a vertical approach would lead to a regime which was industry specific should be determined by the nature of the products; there may be a need for some classes of products in the food chain to be considered together, because of particular public concerns, but generally the food and other industry sectors will involve very disparate products not susceptible to an industry-sector approach.

8. *How do current regulations compare with those of other competitor countries: in Europe; in the Far East; in the USA?*

There is variation within Europe, despite the commonality of the EC directive. Germany and Denmark have been more strict than the UK, while France and Belgium are less restrictive. China is reported to have very little regulation and is allowing large field trials of modified crops. The US regulations are generally less restrictive, with a commercially oriented product-based regime, and with simplified procedures for developments accepted as raising little concern. AFRC has argued strongly with the Department of the Environment for similar fast track procedures in the UK in appropriate cases, and there are currently discussions among EC member states about evolving streamlined procedures.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry?*

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

AFRC's immediate concern is with the effect of regulation on the science base which underpins industrial development. The present regulations are extensive, time consuming and could be costly if they are not interpreted sympathetically where risks are small and as experience is built up; the current cost in the UK for obtaining consent to carry out a release is higher than in some other European countries. The Council is concerned at the adverse effect this could have on research and postgraduate training, with the loss of scientists and ideas. There must be a vigorous UK research base to enable the opportunities of biotechnology to be realised.

Equally, there is a danger that the other elements of the industrial process—from product development through to sales and marketing—will be restricted, which in turn will reduce industrial funding for research if UK industry perceives regulation as being unnecessarily restraining. There is evidence that the regulatory regime in Germany has led to reduced investment and relocation of research and production outside that country to the USA. This danger must be dealt with if the UK is to avoid a similar fate. There is a need for greater international accord in biotechnology regulation.

It is important also that the regulatory regime can adapt to new developments. Plant breeders, for example, will need to evaluate all sorts of genotypes with many inserted genes. The products will not be concerned with one gene in one genetic background. The regulations must meet this situation, and generally be able to deal with likely trends over 10-15 years if industry is to have significant confidence to provide investment.

11. *How best can issues of public acceptance be addressed?*

The AFRC is convinced that public acceptance of biotechnology will be a key factor in getting new developments into practice, perhaps a greater limiting factor than scientific opportunity. The Council is undertaking its own investigations into the determinants of such acceptance, and is involved with other bodies active in this area, for example the Biotechnology Joint Advisory Board.

Public acceptance can be addressed in several ways:

- there should be greater acceptance on the part of scientists of public concern in this area, and more understanding in presentation of research results and in public debate. Universities and institutes must be seen to be regulating their own research, by establishing guidelines for good laboratory practice and in-house safety committees.
- more research on consumer attitudes to biotechnology. The Council has undertaken a study of the public's perception of risk—which is not solely governed by the risk itself but also by their level of concern. At AFRC's Institute of Food Research, there is a major programme on development of models of perceived risks of biotechnology in relation to food products, examination of ethical concerns and the development and testing of communication strategies.
- use of such research to inform public debate. There is considerable media distortion in favour of the risks of biotechnology which must be corrected. Particular sectors of the public, for example in schools, need to be involved. 'Consensus conferences' will help develop the acceptable middle ground.
- every effort should be made to ensure that the regulations in place meet legitimate public concern, but also allow the safe development of products with clear benefits to the public and the consumer, so that confidence in biotechnology can be built up. Successful biotechnology products will help allay public concerns.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

From the AFRC perspective, the main requirement is the maintenance and strengthening of the UK science base in the relevant disciplines underpinning biotechnology. The UK is strong in these areas, but in some cases the UK lead is being gradually eroded as other European countries and Japan catch up. More remains to be done, for example on multigene transfer and gene stability as well as on the wider ecological implications. Greater public funding, and incentives for industrial funding of research, would secure the UK position. This must be linked to increased incentives for the science base and industry to work together, to ensure new developments are taken through to wealth creation, within a regulation regime acceptable to the public. The Government must try to build public confidence in science and technology, including promotion of biotechnology developments, while respecting the legitimate concerns expressed by the public and securing informed risk assessment.

A further factor which could affect competitiveness of UK industry is that of ownership and protection of biotechnological developments. The biotechnology industry has potentially huge markets, particularly those related to genetically-modified organisms, but continued investment in research and development is only justified if the ultimate products are protected. Investment in biotechnology is heavy in the USA partly as a result of the higher degree of protection available there. The draft EC Directive on the Legal Protection of Biotechnological Inventions, currently in draft form, is needed to protect investment by industry and Government. It will harmonise patent law in this area within the EC and improve the UK's competitive position.

Agricultural and Food Research Council

March 1993

Evidence from the Agricultural Genetics Company Ltd

1. *What is your interest in biotechnology?*

AGC was set up in 1983 to market internationally the products of plant biotechnology to agriculturally based industries and organisations. AGC has three businesses through which exploitation of plant biotechnology takes place namely, Cambridge Plant Breeders, MicroBio Division and Business Development Division.

Cambridge Plant Breeders uses a combination of biotechnology and conventional plant breeding to develop and market improved varieties of specified crops. MicroBio uses the results of biotechnology research to develop, manufacture and market naturally-occurring organisms into environmentally acceptable products for both plant nutrition ("biofertilizers") and plant protection ("biopesticides"). Business Development introduces new technology to the market, such as insect resistance genes or the production of animal vaccines in plants, through licensing and collaborative research agreements.

AGC had a turnover of £3·6 million and a loss of £1·8 million for the year 1992. Its spend on biotechnology research and development in 1992 was £1·5 million.

2. *How and why is biotechnology important to UK industry?*

Biotechnology will have a major effect on wealth creation worldwide. The industrial sectors which will benefit most will be health care, chemicals and agriculture. Presently the UK has a strong academic and industrial research base in plant biotechnology which should be exploited. It is likely that the many techniques being developed in other sectors will augment those gained in the agricultural sector and increase the potential use of plants and microbes.

The consumer will gain from a wider choice of plant derived products which have been produced in an environmentally beneficial manner. The use of biofertilizers, biopesticides and genetically modified plants will result in less chemical inputs. In addition, farmers and horticulturalists will gain from having a wider range of crop options many of which will be designed specifically for their end usage.

It is vital for the prosperity of the UK that it exploits this technology and reaps the benefit of innovative products developed using environmentally friendly technology.

3. *What future prospects and opportunities does the technology offer?*

Biotechnology will have a profound effect on the ability to grow plants whose use is more clearly defined whether they are food-stuffs, raw starting materials, biofuels or pharmaceuticals. In addition to possessing a more defined product composition, plants will be genetically modified with improved resistance to pests and diseases so that they require less chemical inputs. Microorganisms will be selected and developed which act as biofertilizers and biopesticides resulting in improved plant performance without the adverse environmental impact associated with chemicals.

4. *What developments in biotechnology raise issues of safety and how should they be addressed?*

In the context of agricultural biotechnology, safety issues are in three areas viz workers, users and consumers of biotechnology products, and releases into the environment. Until 1990 the UK was developing a series of guidelines for a regulatory system protecting both man and the environment. This sensible pragmatic approach was overtaken by the implementation of European Directives 90/219 and 90/220. This has resulted in an over-bureaucratic regulatory regime which has done much to reduce confidence in international investment in EC Member States. Further directives are in preparation from Europe covering all aspects of agricultural biotechnology and presently appear to be overlapping each other.

AGC believes that worldwide genetic modification over the past 20 years has demonstrated an exemplary safety record. In evaluating safety the UK Advisory Committee system, with its members constituted from a wide representation, has provided an effective way of regulating biotechnology and should be continued. Those committees which have direct relevance to agricultural biotechnology are the Advisory Committees for, Genetic Manipulation (ACGM), Release into the Environment (ARCE) and Novel Foods and Processes (ACNFP).

5. *Should biotechnology be regulated by an industry specific regime?*

A biotechnology industry does not exist as an entity but rather as a technology utilised by diverse sectoral groups. Consequently, it is better that regulation for biotechnology is confined within those sectors. New plant varieties, produced by any method would require statutory testing before they can be marketed with clearance under the consent to market requirement of EC Directive 90/220. Naturally occurring microorganisms require experimental permits for efficacy testing prior to licensing. Both plants and microorganisms currently come under MAFF although deliberate releases of plants and microbes require clearance from DoE. It would be most appropriate to have a single Ministry dealing with this sector with an approved risk assessment regime adopted from the present horizontal EC legislation.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than a vertical regulation (where a product is judged by its characteristics)?*

Horizontal regulation is useful only for the regulation of process technology but not for the regulation of specific products. Horizontal regulation is most applicable in the regulation of biotechnology at the laboratory research level. Once the technology has been used to derive the product then vertical regulation should be adopted under the appropriate sectoral regulation as occurs under existing US legislation.

A major reason for vertical regulation is that regulations must be scientifically sound and should recognise the biological differences between animals, plants, bacteria and viruses. One of the difficulties currently encountered with both Directives 90/219 and 90/220 is that neither Directive takes cognisance of those biological differences since the regulations were originally designed with microorganisms in mind. Such differences would be dealt with more effectively using the appropriate sectoral (vertical regulation.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

Yes, but only if the sectoral have not already been put into place. Horizontal regulations are meaningful where the use of the technology evokes safety issues. However, vertical regulation is required where products are being developed or marketed.

8. *How do current regulations compare with those of competitor countries?*

The current regulations affecting the agricultural biotechnology sector are 90/219 for contained use of GMOs and 90/220 for the deliberate release to the environment and marketing of GMOs. Although implementation of these Directives into National legislation should have taken place by October 1991 only a few Member States have of this date managed to do so. The major problem was and is the implementation of Directive 90/220. The UK had to extensively modify the regulations implementing the Directives after a first round of consultation which suggested a series of changes to the format. As a consequence of this consultation, the present UK regulations are usable and the UK can be considered to have interpreted the Directives, steering a middle course as compared to other EC Member States. However, since Directive 90/220 brings a horizontal based regulatory approach to the commercialisation of products it has resulted in a number of problems, which are:

(a) Over bureaucratic. Even though the Directives have yet to be implemented in all Member States at least three are seeking simplified procedures to Directive 90/220.

(b) The various national competent authorities are working with the Commission to develop a workable vertical or product based system by transferring 90/220 into them. Since 90/220 conflicts with some of the existing vertical legislation this will not be straightforward.

(c) The perceived difficulties attached to Directives 90/219 and 90/220 have created a negative impact resulting in a loss of confidence by the financial, industrial an academic communities.

Our major competitors are the USA and Japan who have a product based system of regulations. The USA have not developed special legislation to deal with genetic modification but rather have integrated additional requirements into their sectoral product based regulations. Recently the United States Department of Agriculture (USDA) has proposed that its present system of permits should be replaced by a notification system for field trials for six major crops viz maize, cotton, potato, soybean, tobacco and tomato.

For Japan the oversight of GMO work is carried out using guidance rather than regulation. As in the case of the US the Japanese guidance has been relaxed in a series of revisions since its first implementation in 1979. Japan uses, in contrast to the EC, an extensive system of voluntary review by both industry and the different health departments.

In order to be more specific the following situation is described for three of AGC's areas of interest, namely microbial pesticides, natural fertilizers and genetically modified crop plants. The current situation with microbial pesticides (bacteria, fungi and viruses) is that they are subject to registration requirements in almost all countries whereas biopesticides based on higher organisms (eg nematodes and beneficial insects) are exempt from these requirements in most countries. However, there are significant differences between the USA, where a tier approach to biopesticide registration has been adopted, and the EC. In the USA the first tier of toxicology and ecological/environmental data requirements is relatively simple, compared to the requirements for an agrochemical, and if the date for a new biopesticide are satisfactory then registration is granted without the need for generation of further data. In contrast the data requirements for a new biopesticide in Europe are much closer to those for a new agrochemical. The net result is that registration of a new biopesticide is quicker and less expensive in the USA than in Europe.

The differences become even greater when GMOs are considered. As indicated above the USA regulates the product, not the method by which it was generated, so a biopesticide containing a GMO might not have greater data requirements than one containing a naturally occurring isolate. In contrast the EC regulations for such GMOs is still under discussion but it seems probable that there will be extra data requirements over and above those for biopesticides containing naturally occurring isolates. The impact of these differences will be that significant developments in biopesticides will occur more rapidly in the USA, and that within the European Community biopesticides that do not require registration will be favoured, particularly for small markets.

For natural fertilizers the position is somewhat different since registration requirements in most territories (including the UK) are minimal. This has encouraged the development and sale of inferior, cheap but ineffective natural fertilizers which has damaged the market. The only major countries which have adopted a sensible registration system are France and Canada which should be emulated by the UK.

For genetically modified crops AGC has had to budget for the new costs imposed in the UK by the DoE regarding consent to release and/or market. Such costs appear different in each of the EC Member States as does the amount of information required to obtain a consent. Such information appears to be twice that required by France and more than twice than that in the USA. Moreover, in the US no charges are levied for obtaining a consent to release. As mentioned above, if the US goes to a notification scheme the paperwork will be reduced still further.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards:*

(1) research.

(2) product development.

(3) investment.

(4) location.

(5) sales and marketing?

The harsher regulatory climate in the EC has resulted in multinationals placing their facilities elsewhere. Present statistics (compiled by SAGB), indicate that the USA is attracting a greater investment into biotechnology companies than the EC. As indicated in the answer to Question eight above, stricter regulations in the EC compared to the USA in regard to microbial pesticides and genetically modified crops will certainly drive early product development from the EC into the USA, if not ultimately research. Both the USA public and their attitude towards biotechnological products is regarded as more positive which engenders a willingness by companies to try out their new products there.

Presently it is not clear whether the UK will be disadvantaged compared to other EC Member States by way of investment in biotechnological research. However, in Germany, as a result of the Gene Law and other regulations, several companies decided not to build their biotechnology facilities there but in the US. Currently incoming investment in Europe has largely gone to the Netherlands and Eire.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British Industry of research conducted in the UK science base?*

A majority of AGC's research products have been conducted in the UK through AFRC's research institutes, a number of universities and colleges. AGC is currently transferring that technology derived from those projects into products and licensing opportunities. By supporting projects in this way AGC was tacitly acknowledging that good basic science was being undertaken by such institutions. However, AGC will only support areas of agricultural biotechnology where those UK institutions have some advantage which can be exploited commercially. Owing to the recognised underfunding in the UK science base, institutions hoping to attract industrial support might have increasing difficulties in future years.

An example of a piece of UK research that will not be exploited in the UK is that of a microbial pesticide being commercialised by Ciba-Geigy. This product was developed by AGC in collaboration with Horticulture Research International, Littlehampton and concerns an effective version of the bacterium *Bacillus thuringiensis* which is designed to kill caterpillars on vegetables and other crops. Neither Ciba nor AGC have plans to launch a product in the UK since the market is considered to be too small to justify the time and associated costs for registration.

11. *How best can issues of public acceptance by addressed?*

This is a crucial issue since biotechnology will not be developed by UK industry if the consumer does not want the resulting products. AGC believes that introducing products to the market that have real perceived benefits to the individual rather than to industry, such as gene therapy (cystic fibrosis), cures for cancer, environmental friendly replacements for chemicals and so forth must be the best approach. Owing to the importance of the task it is necessary that industry, academia, government and non-governmental organisations are all involved.

The starting point will be to assure the public of the safety of both the technology and the products. Recent experience has shown that it is essential to ensure that openness prevails and that secrecy, which might give the idea that there is something to hide, should be avoided. Thus the information given should be in non-scientific terms and should highlight the regulatory safeguards and benefits for those products from each sector of biotechnology (eg pharmaceutical, agricultural, food). As the present time the public credibility of science itself is at stake let alone biotechnology, so it is vital that an independent body providing unbiased, factual information.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

(a) Intellectual property rights

In respect to GMOs, the European Patent Office has been allowing broad claims in early patents in this area which could severely restrict future work if licenses from these early plants are not granted. In addition the present EC Directive concerning the patenting of biotechnological inventions is a concern to AGC since it fails to protect it and other seeds industries in areas such as farmers privilege and compulsory licensing.

(b) Government support

The US Government has spent a large effort in examining the support and infrastructure, both financial and regulatory, which are required to exploit the commercial potential of biotechnology. Such support is badly needed from the UK Government to ensure that the foundations laid by both industry and academia are on a firm basis.

(c) Labelling

Great care will need to be exercised to ensure the consumer is well informed on the use of genetic modification to improve food products but is not alarmed. Consequently there must be a sensible system for food labelling involving GMOs. It must be handled in a way that avoids the situation which was unnecessarily created in attempting to implement regulations concerning irradiated foods.

(d) Marketing of GMOs

Work needs to be done at Commission level to ensure that GMOs approved in the UK can freely be sold in other EC Member States. Equally, problems associated with the movement of GMOs (which have consent to market) between the EC and other trading partners must be solved.

Letter to the Clerk from Bayer AG, Pharma Research and Development (Prof. Dr H D Schlumberger)

I would like to acknowledge receipt of your letter of 24 February 1993, explaining the set up of a Sub-Committee to look into the above-mentioned topic. My replies are as follows:

1. *How important does your Government perceive biotechnology to be?*

The Government of the Federal Republic of Germany and especially the Ministry of Research and Technology (BMFT) have clearly stated their interest in the development of modern biotechnology with regard to research and production. This was also demonstrated by the establishment of research programmes on biotechnology and safety research in the past years. The Committee of "Research, Technology and Technology Assessment" and "Health" (Deutscher Bundestag) have initiated the amendment of the German Gene Technology Law after a public hearing in February 1992. It was stated that easing the administrative burdens by the existing law should be achieved in order to support modern biotechnology applications.

2. *Which developments in biotechnology are thought to raise safety issues?*

In contrast to the United States and Japan, recombinant DNA technology is principally considered as potentially hazardous in Europe and in Germany. Europe has adopted a catastrophe scenario of new biotechnology. The safety of biotechnology methods and processes has to be proven case by case in rather complex and time-consuming regulatory procedures. Paradoxically, this has also to be carried out for work with organisms that are classified by definition as harmless (eg group I organisms (Directive 90/219/EEC).

With regard to risks of recombinant DNA technology perceived by the public, the experience of more than 100 years in handling pathogenic micro-organisms ensures a high degree of safety as long as a variety of well proven precautionary measures are observed. Moreover, in thousands and thousands of experiments and productions worldwide, no accidents specific for new biotechnology have been reported. Here again European overregulation contrasts sharply to the American and Japanese approach to biotechnology: recombinant DNA technology does not present risks that are any different from those presented by the unmodified, "natural" host organism. Non-scientific considerations of regulating biotechnology provide a serious barrier for research and scientific education.

3. *In your country, is biotechnology regulated by a specific regulatory regime?*

The German Gene Technology Law (GTL) that implemented the Directives 90/219/EEC and 90/220/EEC, was issued on 1 July 1990. It is supplemented by a variety of regulations to carry out and interpret the provisions of the law. At present, the following regulations are in force or exist as drafts:

1. Regulation about the Central Commission of Biological Safety (ZKBS) (ZKBS-Verordnung).
2. Regulation on the documentation of gene technological projects for reseach and commercial purposes (Aufzeichnungsverordnung).
3. Regulation on safety levels and safety measures of gene technological projects in gene technological installations (Gentechnik-Sicherheitsverordnung).
4. Regulation on public hearings according to the GTL (Gentechnik-Anhörungsverordnung).
5. Regulation on the application for procedures for approval and notification according to the GTL (Gentechnik-Verfahrensverordnung).
6. Regulations of federal fees for activities according to GTL (Bundeskostenverordnung).
7. *Draft:* Regulation for securing liabilities resulting from gene technological projects and deliberate release (Gentechnik-Deckungsvorsorge-Verordnung).
8. *Draft:* Regulation on the participation of authorities of EC member states in the procedure to approve deliberate releases and placing on the market (Gentechnik-Beteiligungsverordnung).
9. *Draft:* Regulation on establishing emergency plans and about liabilities to inform, notify and instruct (Gentechnik-Notfallverordnung).
10. There is a variety of further regulations to be expected, eg, on a simplified procedure for the release of crops, or for the transport of genetically modified organisms.

4. *Do regulations distinguish between contained use and general release (for experiment or marketing)?*

Yes. The GTL and its supplementary regulations distinguish between contained use and general release for both experimental and commercial purposes.

5. *Is regulation in your country "horizontal" (where a product is judged through the process by which it is derived) or "vertical" (where a product is judged by its characteristics)? Which is preferred by your Government?*

The framework of the German GTL implements the structure of the Directives 90/219/EEC and 90/220/EEC that is horizontal. Both research and production of biotechnology is horizontally regulated. In the case of medicinal products, there exists also vertical regulation through the Drug Law (Arzneimittelgesetz).

The Federal Government has made it clear that it will strictly adhere to the EC-Directives. The industry would, of course, prefer vertical regulations.

6. *What are the consequences of your country's regulatory regime on the competitiveness of your firm, in particular as regards*

(1) **Research**

About 80 per cent of all research projects at universities and industry in Germany fall under the biosafety level S1 which by definition does not impose any risks to humans and to the environment. Further 15 per cent are classified to the biosafety level S2 which, according to the state of science and technology, provides only negligible risks for human health or the environment. These two biosafety levels of no or negligible risks are under heavy administrative control and produce bureaucratic burdens that significantly inhibit scientific progress. If the reasons for this burden are analysed, it has to be concluded that the administrative execution of the law certainly contains some "home-made" elements—due to the federal organisation of Germany—but the main reasons are caused by regulations of the "contained use" Directive (90/219/EEC). It is difficult to understand why the handling of genetically modified organisms *per se* is assumed to be dangerous and must be regulated. Risks occur when pathogenic micro-organisms are involved in the experimentation or the production. Moreover, pathogenic micro-organisms remain pathogens whether they are genetically modified or not. Genetic modification of pathogens does not automatically render them more dangerous. Safety assessment is mandatory by the GTL on a case-by-case basis and involves analysis of the elements of each recombinant DNA experiment, ie, the recipient host organism, the vector and the coding DNA sequence that is transferred.

The philosophy to control methods and processes must inevitably lead to an outsized bureaucratic apparatus and in consequence to a slow and costly procedure to control a whole technology field instead of primarily controlling the products where real risks may emerge. This different approach to controlling the potential risks of research methods or production processes certainly impairs European and especially German competitiveness with regard to the United States and Japan.

(2) **Product Development**

Situation is similar as pointed out under "research".

(3) **Investment**

Before the implementation of the GTL, the situation in Germany was very unfavourable with respect to public acceptance of new biotechnology. Projects for production facilities were delayed because of the lack of public acceptance and obstacles caused by the administration and the jurisdiction. Only Thomae Corporation in the state of Baden-Württemberg was able to start the production of recombinant "tissue-type plasminogen activator". The GTL did not significantly change this situation because many regulatory burdens and bureaucratic problems still existed. Hoechst AG has struggled since 1987 for the approval of its recombinant insulin plant. Other companies have moved to the United States for research and production projects.

Bayer AG has decided to produce cell biology-based recombinant medicinal products (eg, recombinant Factor VIII) in Berkeley, California. The scientific and technical conditions of the potential production sites Wuppertal, Germany and Berkeley, California proved to be equal according to an extensive strategic investigation. The legal and general conditions and the chances to achieve an approval of a production facility in a foreseeable time-frame was significantly better in the US than in Germany. This was the determining factor for the decision to invest in the US.

During the past 10 years no foreign biotechnology company has invested in Germany.

(4) **Location**

Bayer has not yet decided the site for production for recombinant products generated in micro-organisms host organisms, ie, bacteria, yeasts. This will depend on strategic considerations, on the scientific and technical conditions and on the legal and general conditions in countries of the triad regions.

(5) **Sales and Marketing?**

As a world-wide operating company, Bayer is marketing its products on an international basis regardless of the production site at which they are manufactured.

7. *Is biotechnology publicly accepted in your country?*

Acceptance of the use of new biotechnology in the medical field (medicinal products, basic research into pathomechanisms) has improved during the past one to two years. This includes also transgenic animals for production of medicinals and somatic gene therapy. With regard to the release of genetically modified organisms, even crops, modern biotechnology is still principally rejected by highly organised, ideology-based groups. There are also exaggerated concerns about "genetically modified" foods.

8. *Has your Government implemented EC Commission Directives 90/219/EEC and 90/220/EEC. If so, how? If not, when do you expect to do so?*

The Directives 90/219/EEC and 90/220/EEC are implemented in the Federal Republic by the Gene Technology Law and a variety of supplementary regulations. The GTL has been in force since 1 July 1990.

I hope that the information will be of help to the Sub-Committee.

Evidence from Professor D R Berry, Head of Bioscience & Biotechnology, University of Strathclyde

This Department has been involved in Biotechnology since the mid-60's when we established a Fermentation Centre and we have continued to have a major research activity in fermentation and enzyme technology since this time. We also teach undergraduate degrees which include a large component of these subjects and have placed graduates in most biotechnology companies.

Although it is the recent developments in molecular genetics and animal cell culture which have received the headlines the basic technologies of fermentation and enzyme technology in particular have wide applications throughout the pharmaceutical and food industries. Our view is that these techniques as well as those of the so-called new biotechnology will have an increasing impact on industries such as the pharmaceutical industry, the food industry, agriculture and environmental industries in the foreseeable future. These are all industries in which we in Britain must maintain a presence and maintain competitive advantage by having state-of-the-art technology both in Universities and in industry. This is particularly true in the pharmaceutical industry where we have several world class companies. The recent developments at ICI indicate that this is also increasingly so in the chemical industry. The separation out of the new company Zeneca from ICI, is an indication of the increasing importance of this sector of the industry.

Whilst biotechnology has thrown up new ethical issues of safety, these have been well handled by the establishment of committees in this country and in other countries. Whilst it is correct that there should be concern about the release of genetically-engineered organisms into the environment and possible long-term effects of upsetting the balance of nature, these should not be exaggerated and it should be fully recognised that much of this work can easily be transferred to countries in the Far East if regulations prevent it happening in the UK. One is already aware of companies such as Pan Labs in Seattle, USA, which contracts most of its experimental laboratory work to Taiwan.

I would not like to comment on the detailed aspect of how our regulations compare to those of competitive countries since I do not have the detailed knowledge. However, my view would be that it is inevitable that there should be an element of horizontal regulation since the risks involved with a product may be concerned with a single stage in its production and possible release at this time rather than the characteristics of the final product. I think we will be looking towards a total quality management approach to these problems where process of involving sensitive techniques will have to be monitored from raw material to product in a manner which is common in the pharmaceutical industry at the present time.

Investment in most areas of biotechnology is a high-cost long-term development which requires a high level of confidence by the industry that the market will be available and profitable in the future. Regulatory uncertainties which could threaten the markets for products of biotechnology could have a serious effect on investment in this area.

It is now recognised that the cost of carrying out state-of-the-art research in these areas is high and that it is unlikely that more than a limited number of University departments will be able to offer state-of-the-art facilities. It is also possible that many strains and procedures may well become so commercially sensitive that they are not available to workers in the University sector. This will force a closer liaison between the major players in biotechnology and the key departments in Universities in training research workers in the appropriate technologies. This is true of the molecular technologies at the present time but will increasingly become true of other areas as developments occur at the interphase between molecular genetics and the more traditional techniques of enzyme technology, protein biochemistry and fermentation technology.

The first two decades of biotechnology have been characterised by a high level of technology push. I believe that this will continue for many more years but there are indications as progress in these technologies could become limited by other factors such as safety and public acceptability. Since I am still of the view that biotechnology represents a major area of growth for the twentieth century it is essential that these legitimate public interests are tempered with a practical need for British industry and Universities to remain competitive in these areas.

Letter to the Clerk from Biocatalysts Limited (SI West Technical Director.)

1. We are the UK's only industrial enzyme manufacturer (British owned). We are a small rapidly growing Biotechnology company with over 60 per cent of our sales going to export.

2. The UK has a lot of scientific expertise in Biotechnology. It is a new technology area that we can compete with the rest of the world. Hence it should become a major part of the UK economy if allowed to develop and grow.

3. The technology offers huge advantages to mankind from agriculture to food to medical. Plus it offers the UK an opportunity to build on its strong scientific base in this area.

4. The main issue is genetic engineering and the production of novel organisms. The issues should be tackled by joint industry/government regulations.

5. The industry should be regulated by an industry specific regime.

6. Vertical regulation is best, it shouldn't matter how something is made as long as it meets certain health and purity requirements.

7. Yes no products should stay horizontally regulated.

8. Europe has stricter regulations. The USA is stricter in some areas, but not all. The Far East has less stringent regulations.

9. Regulation will have no effect on research. Research carries on with little regard to the real world and commercial aspects. Regulations would affect all other aspects.

10. The current regulations are okay and will not prevent exploitation. Any tightening of the regulations would prevent exploitation. Also adopting some of the regulations of the other EC countries would also prevent exploitation.

11. Public acceptance is best addressed by public education. Most of the ridiculous opinions currently held have arisen from a lack of information. A contributory factor has been the unfounded scare stories by the National Press.

12. The main factor affecting UK competitiveness is Government funding going to projects that are of scientific interest to the scientific community and not of any real commercial value. The control of scientific research needs to be taken away from university researchers doing basic research. There is enough government spending on research it just need to be better focussed onto areas that will lead to future market opportunities.

S I West
Technical Director

Evidence from the BioIndustry Association

The BioIndustry Association (BIA) welcomes the opportunity to present evidence on the regulation of UK biotechnology and its effect on global competitiveness.

The BIA is pleased to note that the Select Committee has chosen this topic as a focus for action. In the past the regulatory regime has often been neglected as a major burden on industry's capacity to innovate and compete in world markets.

1. *What is your interest in biotechnology?*

The BIA is the trade association for UK biotechnology companies. The aim of the BIA is to promote a positive environment for the commercialisation of UK biotechnology. Its membership of over 180 includes established and emerging biotechnology companies, small and medium-sized enterprises, and the biotechnology divisions of large organisations. Many of the BIA's principal corporate members are entrepreneurial, high growth, small and medium-sized enterprises which are directly involved in the development and application of biotechnology from all sectors of industry including food, agriculture, pharmaceuticals, diagnostics, human health products, veterinary medicine, plant and animal genetics, energy production and conservation, environmental protection, waste management and equipment manufacture. In addition the BIA has associate members from a wide number of service businesses and institutions which support the corporate members' interests and the BIA's goals.

2. *How and why is biotechnology important to UK industry?*

Biotechnology is the application of scientific and engineering principles to the processing of materials by biological agents to produce goods and services. The application of biological organisms for the benefit of mankind has been widely used for millennia, for example in the production of fermented foods and beverages, the manufacture of cheese and yoghurt, and more recently in the production of antibiotics. However, following fundamental advances in molecular biology over the last 30 years, a range of powerful new techniques is available, such as gene splicing and cell fusion, which dramatically increases the potential applications of biotechnology in industrial sectors. Often the techniquies of biotechnology may be used as cheaper, more efficient and more environmentally friendly production routes for substances already in use.

These fundamental advances have established biotechnology, in a relatively short time, as a key enabling technology in a wide range of industries. Biotechnology has provided tools of unprecedented power for research and for analytical sciences, and has opened up routes to new products, processes and services. It is difficult to forecast the magnitude of its potential impact; however in the US alone, revenues from the biotechnology industry in 1992 were $8.16 billion, growing at a rate of 28 per cent per annum. The UK market was estimated to be $525 million in 1991 with a growth rate above 20 per cent. The world market is projected to grow to $90 billion by the year 2000. These forecasts are based on products specifically attributable to the new techniques.

The discovery in the mid 80s of DNA amplification technologies represented a further major advance which is still having a far-reaching impact in virtually every aspect of the life-sciences. Biotechnology has not reached maturity and the technology is still growing rapidly in power and scope of application.

The UK has made important contributions to the development of biotechnology and to its applications, and is well placed with its strong academic and industrial life science base to continue to contribute and to benefit from further advances.

The UK has a strong position in several of the industrial sectors which will benefit most from biotechnology. Innovation is extremely important to the UK economy for sustainable growth and competitiveness. Biotechnology offers UK industry the best prospect for continued growth in key sectors where the UK already has a pre-eminent position including pharmaceuticals, chemicals, agriculture and foods. Furthermore, it has the strongest sector of emergent biotechnology companies outside of the USA, built on its unique combination of a strong academic science base, availability of entrepreneurial managers and availability of specialist venture capital backers. To date, there have been more than 100 start-up businesses to exploit the excellent science base in the UK (see Appendix 1).

UK biotechnology is an export led market. Approximately 50-60 per cent of revenue for biotechnology comes from exports and foreign investment. Biotechnology companies can be expected to make a substantial contribution to the UK economy and to the balance of payments in the future.

30. *What future prospects and opportunities does the technology offer?*

In principle, biotechnology offers the prospect of revolutionising all industry sectors where the life sciences are, or can be, applied (see Appendix 2).

Biotechnology is having a dramatic impact on many aspects of healthcare, and there is enormous opportunity for companies to provide new products and services to improve health or to treat diseases. This includes the pharmaceutical, diagnostic products and devices industry sectors, and clinical laboratory services sectors. The opportunities extend to the related field of forensic medicine. The UK is strong in several of these sectors.

Biotechnology in medicine and veterinary healthcare has already been used to develop new vaccines, drugs and diagnostic kits. Biotechnology is, in many cases, the only means available for the development and large scale manufacture of a wide range of novel biopharmaceuticals, including therapeutic proteins and monoclonal antibodies, for the diagnosis, prevention, treatment and cure of important medical conditions. Additionally it offers the possibility of engineering proteins and other biologically active biopolymers to improve their therapeutic activities. Currently, recombinant DNA (rDNA) technology has resulted in 16 proteins being manufactured and marketed as pharmaceutical products. Modern biotechnology also has the capability to eliminate many of the risks associated with classical biological products, by removing the risk of adventitious contamination, for example, the removal of the risk of HIV infection in the treatment of haemophilia by the use of Factor VIII produced via recombinant DNA technology rather than by extraction from human blood.

Biotechnology offers the potential for curing a number of single gene defects, and eventually multiple gene defects, with more than 20 biotechnology firms at present engaged in some form of gene therapy research. Work on the human genome project should open increasing avenues for therapeutic intervention.

Biotechnology offers the prospect of better understanding disease mechanisms, providing new molecular targets for drug discovery, and opening up the possibility of a more rational approach to drug design. This will enable better small molecule drugs, with inherent advantages, to be discovered and developed for the many chronic diseases which are currently difficult to treat. Moreover, the products of pharmaceutical biotechnology promise to offer significant cost benefits to the management of healthcare in the UK and other developed countries.

With the world population currently at around 6 billion and increasing at approximately 100 million per annum, the potential for the biotechnology is enormous, particularly in the areas of agriculture and food.

In agriculture there are good opportunities to protect crop plants against pests and diseases, enhance their ability to tolerate adverse conditions such as drought or high salinity, and improve their nutritional value and keeping properties (see Appendix 3). The development of herbicide and pesticide-resistant crops could result in more effective weed control and reduce the use of crop treatment chemicals with benefits to the environment. Crop plants may be used to produce novel feedstocks, replacing those derived from petrochemicals, thus providing a sustainable and much more environmentally friendly resource. More fundamentally, agricultural biotechnology can provide new research tools to strengthen indigenous Research and Development. The UK agricultural biotechnology industry could be a key sector for the penetration of developing markets where the demand for new technologies in sustainable natural resource management is strong and likely to grow.

Transgenic animals are increasingly being developed as important models for research on infectious and genetic diseases, as sources of therapeutic proteins from milk, and as donors of organs and tissues for human transplantation.

There are opportunities in the food industry to improve nutrient quality and flavour and develop new preservation mechanisms as well as to provide analytical tests for food constituents and microbial and chemical contaminants. In processing, the use of more efficient technology will result in energy conservation and less waste production.

In environmental areas there are opportunities to use biotechnology in waste treatment, degrade chemicals in toxic waste, clean up oil spills, control pollution and, in the longer term, generate alternative sources of fuel. Biotechnology has the potential to replace many traditional and chemical intensive industries with more sustainable technology.

There are additional opportunities for companies to provide products, including reagents, instruments and services, such as contract research and development and analytical services to support life sciences research in universities, institutes and industry. The UK has companies with strengths in these sectors.

Fighting diseases, improving the world food supply and controlling pollution are just some of the substantial benefits that biotechnology can provide, thus contributing to the general improvement of the global quality of life.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

The BIA welcomes and supports scientifically-based regulations which are aimed at safeguarding human and animal health and protectng the environment. However, regulation must be subject to scrutiny so that the compliance costs are related to the degree of risk and the time-scale for obtaining a consent is acceptable.

Products manufactured using biotechnology processes usually fall within existing regulatory frameworks that have been developed for the target industry. The techniques of biotechnology are unlikely to raise regulatory issues which have not already been addressed in part by other experience and regulation. In particular the risks from organisms modified by biotechnology are of a similar nature to those risks from the use of unmodified organisms.

The BioIndustry Association fully supports the OECD Council Recommendation of July 1986 which states:

> *"There is no scientific basis for legislation specific to recombinant DNA organisms".*

This recommendation continues to be supported by accumulating experience and scientific evidence.

Gene technology has been developing for the past twenty years and laboratories have always carried out adequate risk assessments, and are now increasingly required to do so by regulation. The early fears surrounding the growth of modern biotechnology have proved, over this period of development, to be without foundation. The biotechnology industry has an unblemished safety record, having had over 1,500 experimental releases of genetically modified organisms and several products in the marketplace with the total absence of adverse consequences. This record is in no small part due to the co-operation and contact between scientists and public authorities, who have worked closely together on a scientific basis to identify possible risks (see Appendix 4).

The experience gained from past and future field trials must be used to evolve appropriate guidelines, rather than keeping to rigid interpretations which may be outdated.

5. *Should biotechnology be regulated by an industry-specific regime?*

The regulation of biotechnology should be commensurate with the scientific indications of potential risk and uncertainty. Biotechnology should not be regulated by an industry-specific regime, but the *products* of biotechnology should be so regulated on the basis of safety, efficacy and quality in those industries whose products, services or activities *require* regulation. Industry will thereby benefit from the application of relevant knowledge and experience to tackle the many applications of biotechnology processes. A model of this approach can be seen in the USA where novel products are being brought rapidly, safely and cost-effectively to the market.

The Commission of the European Communities clearly advocated a similar approach of sectoral legislation in its April 1991 communication, "Promoting the Competitive Environment for the Industrial Activities Based on Biotechnology within the Community", SEC(91)629; subsequently re-published (without annexes) as one of the three communications in the Bulletin of the European Communities, Supplement 3/91, "European Industrial Policy for the 1990s". In the Commission's original proposal for the contained use and deliberate release directives this was also the case. Unfortunately, the approach towards sectoral legislation was changed during the process of negotiation in the European Parliament and Council of (Environment) Ministers. Academic and industrial interests at European and national level were systematically excluded from this debate.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

Vertical regulation is certainly to be preferred, for the reasons indicated above. The industries where biotechnology is likely to have the greatest impact are already regulated through extensive existing product legislation. It is essential to avoid discriminatory regulatory requirements for biotechnology processes and products which would constitute a systematic and in-built discrimination against innovation, in particular against inherently safer technology (see Appendix 5).

It is important to firstly consider the nature of the products or effects of the activities. "Horizontal" legislation is valid for cross-cutting concerns such as worker safety, animal welfare, patent laws, taxation rules etc. In many cases satisfactory mechanisms are already in place to protect man and the environment within current legislation, and there may not be a need for further horizontal regulation.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

In general, horizontal regulation may be appropriate in the research and development stages, but having established the consistency and characteristics of the product, regulation should be vertical, in those cases where the product (or services or activities) require regulation.

It is important for a single regulatory agency in any given sector to manage the evaluation of safety, efficacy, purity and impact on the environment in the approval pathway for marketing new products in that sector. If these review processes are separated, and become the responsibility of different regulatory agencies, the impact may be to delay delivery of the benefit of the product and would, in the longer term, militate against innovation in these types of technology.

8. *How do current regulations compare with those of other competitor countries?*

In Europe

The Deliberate Release and Contained Use Directives were established to harmonise regulation within EC countries. However in the adoption of the two Directives there has been wide variation in the manner of interpretation. Any variation in the interpretation of Directives is potentially damaging to UK competitiveness. Implementation in Germany was by means of the 1990 Gene Law which has been found to be excessively restrictive by industry and academia. In 1992 the Bundestag decided to revise this law including, if necessary, requesting changes in the EC Directives.

In the Far East

Japan's biotechnology industry is controlled by a system based on guidelines rather than regulations. An attempt (at the suggestion of the Commission of the European Communities Directorate General XI: Environment, Civil Protection and Nuclear Safety) to introduce the Deliberate Release and Contained Use style of Directives in Japan's Diet was withdrawn in 1991. The tremendous investment in biotechnology by the Government has resulted in a pragmatic approach to oversight, but certainly still characterised by great caution; eg a five-year moratorium was imposed by the Ministry of Agriculture in the early years of single-cell protein development, largely because of public fears and uncertainties.

In the USA

The US White House policy on regulation states: "products developed through biotechnology processes do not *per se* pose risks to human health and the environment". This approach is being woven into the public fabric of the USA—it is clear that the US is approaching a product based system of regulation, and that it is leading the world in this respect. The Federal regulatory policy aims to encourage investment in innovation and technology development by developing regulations which involve the lowest possible cost of compliance. Extra Federal funding has been allocated in the 1993 US review budget for the further development of the regulatory review processes.

The 1993 US Biotechnology Research Initiative recognises the need for closer integration between the three government agencies which have the principal regulatory authority in the USA. These are the Food and Drug Administration (FDA), the US Department of Agriculture (USDA) and the Environment Protection Agency (EPA).

The rapidly increasing number of permits issued for the testing of genetically engineered plants in field trials indicates a progressively more efficient and less restrictive regulatory climate that existed formerly in the USA. Rule-making powers under existing statutes are being used to allow flexibility and adaptation to progress of knowledge—eg the USDA new rules. This trend is *not* being significantly altered by the new Administration: the Clinton-Gore Technology Paper of 22 February emphasises biotechnology, and speaks of "reducing the cost of regulatory compliance". The FDA suggests that the new biotechnology techniques are considered to be extensions, or refinements, of older techniques and subject to the same regulatory paradigms, procedures and jurisdictions.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards:-*

General

The consequences of excessive or restrictive regulation would mean that the UK capability in biotechnology would be increasingly eroded, scientific and technical leadership lost, and the competitive position progressively weakened. If the UK regulatory climate becomes relatively unfavourable then the most able British scientists and technicians may emigrate to more fertile pastures, while companies could opt for direct investment in research, development and manufacturing facilities in countries other than the UK, where tax benefits, combined with an adequate science base, can be an attractive alternative.

Research

A bureaucratic regulatory regime may result in the escalation of research costs and may restrict the speed of innovation and development emerging from the UK public and industrial science base.

It is clear that any increase in the regulatory bureaucracy will put the UK at a significant disadvantage. We already see job applicants from Germany who specifically come to work in the UK due to problems in biotechnology within their own industry. A similar "brain drain" could easily be caused by inappropriate legislation in the UK. There is a further danger that the pace of research could be slowed unless Government Departments are able to process notifications and consents for biotechnology projects in an expeditious manner.

Product development

Investment by UK and off-shore corporations in commercial development and manufacturing infrastructure may gravitate to countries with a more balanced regulatory system. It is essential that the UK regulatory organisations are adequately resourced to avoid delays in the processing of applications for product licences.

The restrictive regulatory regime in Germany resulted in some companies conducting product development elsewhere eg Hoechst went to the US, Australia and Japan for pilot-scale production of certain biological molecules.

Investment

Some of Europe's pharmaceutical majors are investing in product research, development and manufacturing infrastructure almost entirely outside of Europe whilst marketing their products within Europe. For example, BASF has built its corporate R&D facilty in Worcester, Massachusetts. Ciba Geiby has chosen to locate its new £100 million manufacturing plant in France which appears to have a more sensible regulatory framework than Switzerland, where the company has its headquarters. Boehringer Mannheim has just announced it will build a new therapeutic protein plant in Ireland, probably due to a more reasonable regulatory environment and attractive tax benefits and subsidies from the Government.

Location

Of the US companies choosing to locate offices or manufacturing facilities in the EC, many have chosen The Netherlands for regulatory and tax inducement reasons eg Synergen, EuroCetus (Chiron), Centocor. About 50 US biotechnology companies have located their marketing and distribution offices in the UK, but not necessarily their manufacturing and R&D facilities (see Appendix 6). Two American companies, Creative Biomolecules and Panlabs actually suggested that a hostile regulatory climate prevented them from locating in the UK.

Sales and Marketing

Although the majority of product development for biopharmaceuticals has, to date, taken place in the US there has been no barrier to those US companies entering the European market. Germany, despite its perceived opposition to genetic engineering, has approved the marketing of products made by genetically engineered organisations faster than anywhere in the world, including the US and Japan. Germany's lead in the introduction of biopharmaceuticals is surprising in light of the fact that biotechnology faces by far the greatest societal resistance. On the other hand Germany seems to benefit the most from new medical opportunities derived from this technology. For Germany, as for the UK, it is unfortunate that the profits from the sales of currently marketed products are US-bound.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

It is important that proper regard is given to the overall impact of regulation, as regulation which is over bureaucratic can place excessive burdens on business and universities. Regulation must strike the balance between essential protection for the public and the environment, and over-zealous, intrusive, and expensive controls aimed at the elimination of all conceivable risk. It would be sensible to see a Compliance Cost Assessment (CCA) when considering any proposed regulation, which takes into account the timescale for obtaining a consent.

It is important that conditions for research and development in the UK remain competitive with those elsewhere in Europe and, especially, with the USA in order to prevent a UK to US "brain drain". The new legislation on release and consent to market may mean that some companies will go to other EC countries for approval where it is more cost effective and easier to obtain approval. It should be the aim of the UK Government to ensure that harmonisation of the EC Directives does not leave UK companies disadvantaged, and to ensure that the most cost effective system in Europe is instigated while maintaining appropriate regulatory standards, thus encouraging companies to seek approval in the UK.

It must also be borne in mind that if the research activity in one field is curtailed by over regulation it will have knock-on effects in other areas. The uncertainty which exists in the UK over marketing, labelling and the acceptance of products makes it very difficult to obtain support for the research and development of valuable technologies and products.

It is suggested that the UK government should establish a specific mechanism and timetable for the review of the UK regulatory regime for biotechnology with the objectives of:

(a) improving existing legislation in the light of experience (eg by appropriate simplification);

(b) ensuring that legislation keeps in step with acceptable developments outside the UK.

The procedure should include provision for consultation between relevant parties, including industry and academia. The BIA would wish to participate in the review process.

11. *How best can issues of public acceptance be addressed?*

The growth of biotechnology in the United Kingdom and the maintenance of its international competitiveness depends not only upon successful research and development, but also upon the existence of a healthy relationship between the biotechnology community and the general public. If products do not sell, or are not expected to sell, then they are not produced and the foregoing investment in R&D is wasted or not undertaken. The understanding and acceptance of biotechnology by the general public is fundamental to the future success of biotechnology companies.

At present, the level of public understanding of biotechnology is generally low although it has become an increasingly topical subject for the mass media, which, for the general public, is the dominant source of information about new developments. Unfortunately, presentation of information by the media is not always objective and there have been many examples of biased or mis-informed reporting. Moreover, biotechnology appears to be faced with growing apprehension and antagonism led by a number of pressure groups which have already had notable success in Germany and, to a lesser extent, in the USA, Denmark, Switzerland and The Netherlands.

Many opinion polls of public attitudes to biotechnology have been carried out in the UK, Europe and the USA over a number of years. All concur in showing that the general public continues to have mixed and even contradictory feelings about biotechnology, coupled with low levels of knowledge.

There is clearly a great need for a coordinated programme to ensure that the public has an accurate understanding of biotechnology. It is essential for the general public to develop their views in a balanced way through open debate and this will only be acheived by provision of reliable information. All attempts towards dialogue and provision of such information are to be welcomed. Efforts are already being made especially by the private sector in the UK and elsewhere to improve this situation. The European Commission provides financial support to projects which aim to increase public awareness and understanding of biotechnology. In the UK the Biotechnology Joint Advisory Board has the improvement of public perception of biotechnology as part of its overall strategy.

Government, by its actions, will strongly influence public perception and acceptance of biotechnology, particularly genetic modification and related technologies. It is essential to ensure that the public knows that a balanced and scientific regulatory system is in place and that it is being effectively implemented. However, it is also essential to communicate to the public that the regulatory system is constructive and facilitatory, ensuring quality and requisite performance of a product and confirming its safety, and not that the regulation is required because biotechnology products are inherently unsafe.

Information relating to regulation and control must be provided according to the principle of transparency as far as is commensurate with the protection of intellectual property rights and commercial confidentiality.

Consideration needs to be given to five main areas of communication:

(a) Between government agencies, industry and academia;

(b) Between the biotechnology community and the non-specialised general public;

(c) Between the biotechnology community and specialised groups such as opinion leaders and decision makers, journalists and TV/radio producers, teachers and college lecturers, environmental and consumer groups, etc;

(d) Throughout education, particularly at the schools and college levels and in relation to the National Curriculum, teacher training and the provision of teaching and experimental resource materials;

(e) Further research where required to supplement the already existing body of knowledge to develop greater understanding of the mechnisms of public perception and communication in biotechnology.

At present, public awareness issues are being dealt with by a number of groups in the UK and Europe (eg the European Commission, the European Federation of Biotechnology Task Group on Public Perceptions of Biotechnology and the UK Biotechnology Joint Advisory Board). As the issues which need to be addressed are diverse, it is not possible for an individual organisation to provide a coherent strategy for action. However there is need for the creation of a single co-ordinating task force on the public understanding of biotechnology to include representatives of Government, industry, communications experts, the media, educationalists, interest groups and the target audiences. The Biotechnology Joint Advisory Board of the DTI and Research Councils might well provide the nucleus for such a grouping based on its already conducted strategic planning exercises.

The creation of such body would serve to ensure that public and industrial resources are used to best advantage without duplication for the provision of objective, independent and authoritative information and the encouragement of effective dialogue between the biotechnology community, government, the general public and public interest groups.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

Patents

The protection of intellectual property and international patent rights are important factors in promoting competitiveness. Within the EC there is a lack of uniformity of patent law in the biotechnology field resulting in uncertainty as to the strength and value of biotech patent rights. In the USA where the biotechnology industry is more competitive, a more favourable patent environment exists for biotech invention. The discrepancy between the position in the EC and that in Japan and the USA has been recognised by the European Commission through a draft Biotechnology Directive which would have gone some way to putting the EC biotech industry on the same footing as that in the US and Japan. Unfortunately, it has been hijacked by a number of groups pursuing vested interests, particularly those claiming to represent the interests of farmers, plant breeders and animal rights. As a result, the original objective of the Directive has long been lost. It is preferable that the draft Directive be not enacted at all rather than be enacted in its present form.

Education

Education and training are crucial issues in biotechnology, which is characterised by the generally high skill and qualification levels of the majority of its personnel, and by its multidisciplinary and academic nature. The opportunities offered by biotechnology cannot be realised unless the essential human resources are available.

There have been many surveys of manpower and training needs for biotechnology and generally they point to selective recruitment problems for industry. Considerable increase in demand is anticipated by industry for scientific updating, conversion training, induction training of new personnel and awareness training of non-scientific staff. There is high and unsatisfied demand for training specifically designed for biotechnology in key areas of management function. The number of advanced courses is more or less sufficient, rather the need is for cost-effective courses closely or flexibly designed for their specific purposes, including open and distance learning courses.

Finance

Biotechnology companies require adequate financial resources from seed funding and venture capital in the early stages of a company's existence, through development capital once it has established itself, to the public equity markets to provide liquidity for early investors and to access larger amounts of capital. These are critical for the successful development and competitiveness of the UK biotechnology industry. The more difficult it is to attract funds at each stage, the slower will be the development of companies. This will in turn lead to a loss of international competitiveness, particularly compared with the USA where such funds are more widely available than in UK.

The BIA considers the following areas are relevant in this respect:

(a) Fiscal incentives designed to encourage entrepreneurial activity would help to attract funding to new ventures in the sector. The measures in the 1993 Budget allowing capital gains tax on the sale of shares in private trading companies by individuals to be deferred to the extent that the sale proceeds are reinvested in another such company are welcomed, as are the relaxation in the conditions for retirement relief on qualifying private company sales.

(b) The reduction in the levels of interest rates has reduced the general levels of return on "risk free" investments and correspondingly increased the premium derived from investments in biotechnology companies, thus making such investments relatively more attractive. Sustained low interest rates are of benefit to the sector.

(c) The size of the UK Public Sector Borrowing Requirement and its relationship to institutional cash flow has in some instances reduced the sums available for institutions to invest in unquoted equities. This makes it more difficult for companies to raise the funds they require in the UK.

(d) It is necessary for biotechnology companies to provide an exit mechanism for early investors and also to raise additional funds for further development. The BIA welcomes the recent proposed changes to the listing requirements of the London Stock Exchange, and also its recent announcement that it is to delay the closure of the Unlisted Securities Market and is to investigate "the future capital requirements of companies which are outside the scope of the Official List".

Biotechnology companies have recently been successful in accessing both public and private equity markets in the USA. This increases the alternative sources of funding available to them, but increases the competitive advantage of US biotechnology in having a larger national funding base.

The BioIndustry Association would also like to explore with Government Departments:

- The adoption in the UK of some of the mechanisms developed in the "VALUE" programme of the European Community to support investment by institutions and large companies in the exploitation of high technology R & D by small to medium sized enterprises. The Community has included mechanisms to define "high technology".

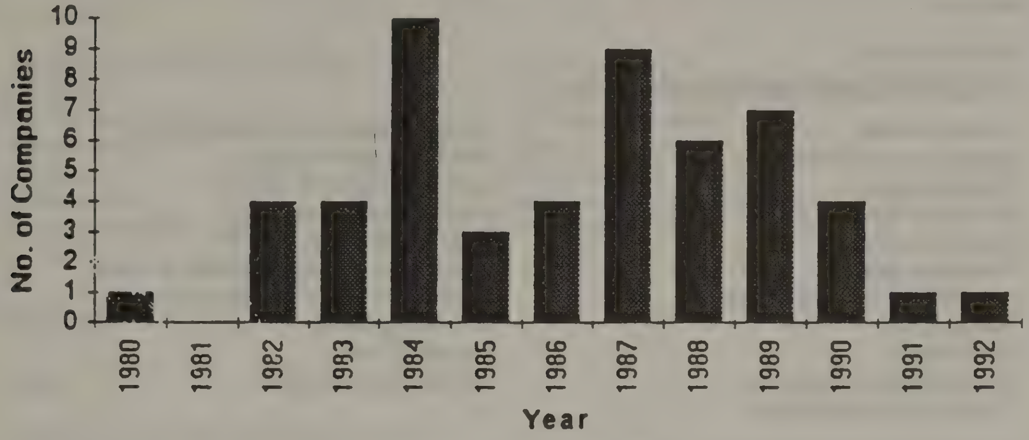
— The extension of the Enterprise Zone concept to an Enterprise Industry concept in which the regulatory, funding and taxation burdens could be lightened for specific, development-intensive industries, for a specified period of time and up to specific limits of support. The US initiative on biotechnology has fostered, amongst other measures, state funded industrial revenue bonds, which underwrite up to 75 per cent of the investment needed for biotechnology production plants.

— The further consideration of the BioIndustry Association proposal contained in its earlier submission to the Office of Science and Technology, concerning the forthcoming White Paper, which called for the implementation of negative corporation tax on development expenditure in such an Enterprise Industry.

That earlier submission exemplified also the activities of the State-funded North Carolina Biotechnology Centre, which has an annual budget of $7.8 million to support the earliest stage of technology transfer, in which a concept is tested for technical and commercial feasibility, to the stage where it can attract venture capital.

APPENDIX 1

A—CHART SHOWING SOME NEW BIOTECHNOLOGY BUSINESSES STARTED UP SINCE 1980



The total number of employees for the above 54 biotechnology businesses that have started up since 1980 is approximately 5,000.

The UK Biotechnology Handbook (1993) lists 678 UK organisations of which there are:

363 companies using biotechnology directly
149 service companies providing support to the industry
25 institutions which provide investment support to the industry
113 academic institutions connected with the industry

B—LIST SHOWING SOME NEW BIOTECHNOLOGY BUSINESSES STARTED UP IN THE UK SINCE 1980

Affinity Chromatography
Agricultural Genetics Company Ltd.
AgriSense-BCS Ltd.
Anagen Ltd.
Antisoma Ltd.
Archaeus Technology Group Ltd.
Biocatalysts Ltd.
Biocode Ltd.
Biocompatibles Ltd.
Biocure Ltd.
Bio-Flo Ltd.
Biomet Ltd.
Biopharm (UK) Ltd.
Bioprocessing Ltd.
Bioscot Ltd.
Biosyn Ltd.
Biotal Ltd.
Biotrace Ltd.
British Biotechnology Ltd.
Cambridge Antibody Technology Ltd.
Cambridge Bioscience Ltd.
Cantab Pharmaceuticals plc.
Celltech plc.
Celsis Ltd.
Chiros Ltd.
Cogent Diagnostics Ltd.
Danbiosyst UK Ltd.
Delta Biotechnology Ltd.
Enzymatix Ltd.
Guildhay Ltd.
Helix Biotechnology Ltd.
Jaytee Bioscience Ltd.
Marshall Biotechnologies Ltd.
Medeva plc.
Mercia Diagnostics Ltd.
Mycoplasma Experience Ltd.
Mycotech Ltd.
Oxford Glycosystems Ltd.
Oxford Molecular Ltd.
Pharmaceutical Proteins Ltd.
Plant Science Ltd.
Omega Diagnostics Ltd.
Quadrant Holdings Cambridge Ltd.
Quantum Biosystems Ltd.
Quatro Biosystems Ltd.
Polyfiltronics Ltd.
Quest International (UK) Ltd.
Seralab Ltd.
Serotec Ltd.
Scotgen Pharmaceuticals Ltd.
Scotia Pharmaceuticals Ltd.
Shield Diagnostics Ltd.
Viridian Bioprocessing
Xenova Ltd.

APPENDIX 2

SOME BIOTECHNOLOGY PRODUCTS AVAILABLE AND BEING DEVELOPED

1. MEDICINE

1.1 *Pharmaceuticals*

Therapeutic Proteins and Growth Factors

Human insulin
Human serum albumin
Erythropoietin
Interferon alpha
Interferon beta
Interferon gamma
Lymphoblastoid interferon
Interleukin-2
Interleukin-6
Human growth hormone
Epidermal growth factor
Transforming growth factor alpha
Fibroblast growth factor
Insulin-like growth factor1
Colony stimulating factor
Ciliary neurotropic factor
Granulocyte colony stimulating factor
Granulocyte macrophage colony stimulating factor
Soluble CD-4s
Tumour necrosis factor

Anticoagulants/Thrombolytic Agents

Tissue plasminogen activator
Factor VIII
Factor IX
Factor XI

Monoclonal Antibodies

OKT3 antibody
Anti myosin
Anti carcinoembryonic antigen
Anti T cell (CD-3)
Anti T cell (CD-4)

1.2 *Vaccines*

Human

Viral

Epstein-Barr
Cytomegalo
Hepatitis A
Hepatitis B
Hepatitis C
Human Immunodeficiency (HIV)
Influenza
Polio
Papilloma
Rotavirus
Varicella zoster
Herpes simplex

Bacterial

Cholera
Leprosy
Pertussis
Tetanus
Typhoid
Typhus

Parasitic

Malaria
Schistosomaisis
Sleeping sickness

Other

Fertility regulating

Animal

Viral

Rabies
Pseudo rabies
Infectious bovine rhinotracheotis
Rinderpest
Foot and mouth disease
Feline leukaemia
Feline immunodeficiency
Rotavirus (anti scours)

Bacterial

E Coli
Anti scours

1.3 *Gene Therapy*

Somatic cell defects

Germ cell defects

2. DIAGNOSTICS

Immunoassays using monoclonal antibodies
Non radioactive detection in immunoassays
Imaging
DNA probes
Polymerase chain reactions

Applications for:
Human and veterinary medicines
Infectious diseases
Genetic diseases
Food hygiene
Agriculture and horticulture
Forensic science

3. AGRICULTURE

3.1 *Animal*

Animal nutrition and growth promotion

Feed additives

Growth hormones

Animal breeding

Identification of desirable genes and gene products

Transgenic animals

3.2 *Plant*

Plant productivity

Resistance factors; insect, viral and fungal
Seed improvement
Secondary plant products
Plant growth rate

Photosynthetic efficiency
Plant-produced pesticides
Bacteria-produced insecticides
Stress resistance (drought and salinity)
Improvement of keeping properties

Use of micro-organisms for crop improvement

Nitrogen fixation
Mycorrhiza

Microbe-produced pesticides
Microbes that can influence plant growth

Other applications

Microbial silage inoculants

Slurry digesters

4. FOOD

Nutrasweet
Renin

Cheese made using genetically engineered chymosin
Lipase

5. ENVIRONMENTAL

Waste treatment

Improvement of conventional treatment processes
Control of heavy metal contamination

Control of organic micro pollutants

Toxic waste treatment
Methane production

Microbial Mining

Mineral leaching

Metal concentration

Other

Microbial enhanced oil recovery
Pollution control
Bioremediation

Biosensors
Biomaterials

6. INDUSTRIAL

- Snow-Max, ice nucleation
- Chemical intermediates from plant tissue culture and fermentation
- Biopolymers
- Biocomputers
- Machines eg fermenters, containment facilities, DNA sequences, centrifuges, electrophoresis etc
- Software for protein/DNA structure
- Journals and publishing

APPENDIX 3

(A) MOST COMMON TRAITS EXPRESSED IN TRANSGENIC PLANTS TESTED IN THE FIELD FROM 1986 TO 1991

Type of the Major Gene of the Construct	*Target Family*	*Number of Crops*	*Number of Field Trials*
Herbicide gene	Glufonsinate	11	77
Herbicide Tolerance	Glyphosate	9	37
Herbicide Tolerance	Sulfonyureas	9	21
Insect resistance	Bt toxin	10	42
Virus resistance	Potato viruses	1	19
Virus resistance	Tomato viruses	1	10
Product quality improvement	Male sterility	5	20
Product quality improvement	Seed storage protein	5	9
Market gene	Kanamycine resistance	9	36

(B) NUMBER OF DIFFERENT CROPS INVOLVED IN FIELD TRIALS FOR A PARTICULAR TRANSGENIC TRAIT, STARTED IN 1991 OR TESTED IN 1991 AS A CONTINUATION OVER SEVERAL YEARS

Type of the Major Gene of the Construct	*1991*	*1990-91*	*1989-91*	*1988-91*	*1987-91*	*1986-91*
Virus Resistance	5	6	3	2	0	0
Disease Resistance	4	1	0	0	0	0
Insect Resistance	5	2	1	1	0	1
Herbicide Resistance	8	4	4	5	2	1
Product Quality Improvement	6	0	3	1	0	0
Total:	28	13	11	9	2	2

APPENDIX 4

(A) NUMBER OF APPROVED FIELD RELEASES OF TRANSGENIC PLANTS, BY COUNTRY

Country	*Number of Releases*	*First Year*
Argentina	3	91
Australia	1	91
Belgium	42	87
Canada	52	88
Chile	3	87
China	2	91
Costa Rica	1	91
Denmark	5	90
Finland	5	90
France	83	86
Germany	2	90
Israel	1	91
Italy	2	89
Japan	1	91
New Zealand	7	88
Spain	7	88
Sweden	4	89
Switzerland	1	91
The Netherlands	12	88
United Kingdom	19	87
United States	141	86
21 Countries	Total = 394	

(B) NUMBER OF APPROVED FIELD RELEASES OF TRANSGENIC PLANTS, BY CROP SPECIES

Crop Species	*Number of Releases*	*First Year*
Alfalfa	18	88
Apple	1	91
Asparagus	1	88
Birch	3	90
Cauliflower	1	91
Chicory	1	91
Chrysanthemum	2	91
Cotton	15	89
Cucumber	3	89
Flax	8	88
Lettuce	1	91
Maize	21	90
Melon	5	90
Oilseed rape	72	87
Petunia	2	90
Poplar	8	88
Potato	71	87
Rice	4	90
Soybean	8	89
Squash	2	90
Sugar Beet	19	89
Sunflower	1	91
Tobacco	76	86
Tomato	49	87
Walnut	2	90
25 Species	Total = 394	

APPENDIX 5

'BIOTECH DIRECTIVES AND REGULATIONS OF THE EUROPEAN COMMUNITY

Production and use of biotech-derived products

Directive on the protection of workers exposed to biological agents (1990)
Directive on the contained use of geneticaly modified organisms (1990)
Directive on the deliberate release of genetically modified organisms (1990)
Directive for placing on the market biotechnology medical products (1987)
Regulation for production refund on sugar products used in industry (1986)

Juridical protection of intellectural property

Directive proposal on legal protection of biotechnological inventions
Regulation proposal on supplementary protection certificate for medical products
Regulation proposal on community plant variety rights

Some proposals being considered by the Commission

Novel foods, food ingredients and processes
Genetically modified animals
Transport of biotechnological organisms and micro-organisms
Animal productivity enchancers

APPENDIX 6

US BIOTECHNOLOGY SUBSIDIARIES SET UP IN THE UK

Alltech Inc.
American Biotechnologies Inc.
Amgen Inc.
Amylin Pharmaceutical Inc.
Applied Bioscience International Inc.
Applied Biosystems Inc.
Atlantic Antibodies Inc.
Atlantic Antibody Inc
Bachem Inc.
Ball Research UK Ltd.
Beckman Instruments Inc.
Bio-Rad Laboratories Inc.
Biogen Inc.
BioWhittaker Inc.
Cambridge Neuroscience Research Inc.
Cel-Sci Corp.
Charles River UK Ltd.
COBE Laboratories Inc.
Collagen (UK) Ltd.
Diagnostic Products Corp.
EuroCetus
Gensia Europe UK Ltd.
Genosys Biotechnologies
Genzyme
Gibco Division
Granada Bioscience Inc. UK
ICN Biomedicals Inc.
Idex Laboratories Ltd.
Incstar Ltd. UK
Intergen Co.
Lifetechnology UK Ltd.
MediSense UK Inc.
Microbiological Associates
Molecular Design Ltd.
New Brunswick Scientific (UK) Ltd.
Oncolab Ltd.
Ortho Biotech Slough UK
Peninsula Laboratories Europe
Polybac Europe Ltd.
Polyfiltronics
Quality Biotech
Quintiles
Rohm & Hass (UK)
Senetek plc.
Synthex Pharmaceuticals
Therapeutic Antibodies
TSI
Vector Laboratories

Evidence from Professor D Boulter, Department of Biological Sciences, University of Durham

1. *What is your interest in biotechnology?*

Crop improvement via plant biotechnology.

2. *How and why is biotechnology important to UK industry?*

It is generally agreed the biotechnology will have a significant impact in the Biosciences industries by the turn of the century and a major impact by the second decade of the next. The UK has, on the one hand, the science and basic know-how and, on the other, the industrial base to enable the UK to take a goodly share of these new opportunities.

3. *What future prospects and opportunities does the technology offer?*

Prodigious opportunities in medical, agrochemical, food, and other bioindustries.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

Genetic Engineering, a major development, raises environmental, safety and ethical issues, which are best addressed in open forum conducted by "trusted" organisers, involving the various interested parties (environmental and consumer groups, industry, the public at large) and not confined to so-called experts in the field.

5. *Should biotechnology be regulated by an industry specific regime?*

Probably not.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

No-vertical regulation is better, but strict product characterisation is then essential.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

In my view, not necessary (see 6).

8. *How do current regulations compare with those of other competitor countries in Europe, in the Far East, the USA?*

Regulations vary still in Europe, although this should soon change. Up until now countries like Germany and Denmark, have been stricter and countries like Italy and Belgium less strict than the UK The USA has much laxer regulations.

9. *What are the consequences, likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards*

If UK industry perceives regulation as unnecessarily constraining, research (they are major players), product development, investment, sales and marketing, will be curtailed. Examples of community countries locating factories elsewhere, i.e. not in Germany or Switzerland, exists.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

The case-by-case UK approach is satisfactory if it is managed by the regulatory authorities in a sympathetic manner. It is especially important to identifying when a particular requirement might pose great hardship and to work with industry to resolve difficulties.

11. *How best can issues of public acceptance be addressed?*

It should be impressed on public sector scientists that communicating their results to the public in an understandable manner is part of their responsibilities. Research Councils and universities have some responsibility in ensuring some training in this matter. Scientists engaged on biotechnology research should then, on a local basis, involve themselves in public debate.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

Maintaining an innovative science base and increasing the effectiveness of technology transfer particularly from the public sector science base and SEM's.

EXECUTIVE SUMMARY

Biotechnology offers prodigious opportunities in the bioscience industries and the UK has the potential to take a good share of these, providing well-balanced regulations are put in place and public acceptance issues addressed.

Evidence from Professor Sydney Brenner FRS, School of Clinical Medicine, University of Cambridge

As you know, I am now not able to attend the Sub-Committee on the morning of April 29, as I have to go to America that day. I am therefore sending you a written note of the most important things I would like to say in regard to your enquiry.

I was very much involved in the process initiated in 1974 to deal with the regulation of genetic manipulation in biological research. That began with the mistaken concept that organisms, which had been altered by *in vitro* manipulation presented intrinsic risks that could be scaled by the nature of the DNA inserted into the vector host systems required to clone the genes. After some years of debate, this totally illogical and unrealistic way of dealing with conjectural risks was altered, and the total genetically modified system was treated as the entity. The conjectural risks and any measures taken to deal with them were assessed on a scale that took real risks as the basis. On the original system, cloning lion DNA was though to be a greater risk than cloning pussycat DNA because lions are clearly more dangerous than pussycats. We now do not think that way, because clearly both kinds of DNA when cloned are harmless because there is no way that the original pathogens could be assembled from an ensemble of clones. We should be reminded that the most dramatic consequence of this change in thinking was that work on determining the structure of the AIDS virus and all subsequent research proceeded very rapidly, because it was realized that cloning the virus into a bacterial host actually *attenuated* pathogenicity over that of inflected blood, for example, and while the modified bacterium still has to be compared to an unmodified one; this can be dealt with by simple measures.

Thus, in the cases where regulation is required, I believe we should judge biotechnology products of their *properties,* within the environmental or industrial context of their application. The mode of derivation of the product may be relevant to that judgement in some cases, where it is part of the manufacturing process, for example, and it would then need to be taken into account. I therefore support what you call the vertical approach as apposed to the horizontal approach.

Biotechnology is already an important component of the pharmaceutical industry, and its importance will increase as research and development in this and related life science industry comes more and more to depend on the methods of molecular biology and genetics. It has been estimated that worldwide research and development in the pharmaceutical industry is worth at least 25 billion dollars annually—about 12 per cent of the pharmaceutical industry itself—and it is an important activity to retain and even expand in the UK.

In Germany (and also in Switzerland), the climate has become very unfavourable for research and development in this field because of unreasonable regulation and public attitudes, so much so, that most Swiss and German pharmaceutical groups have moved a considerable fraction of their R & D (and, in some cases, their production) facilities to the United States. Since most of these companies are multinational, they will choose to operate in those countries where the climate for research, development and investment is the most favourable. The UK has been a very small recipient of such investment, not because of an adverse regulatory system but because the past decade of decline of the UK research base in this field has not made this country as attractive as others.

In considering regulation we should carefully distinguish between what we need to do for objective scientific reasons and what we feel we should do for social and political reasons such as satisfying the public perception of a technology or even public attitudes to science and technology in general. It is extremely important that rationality in the field of regulation must be accompanied by public education in order to explain the issues and thereby achieve wide acceptance and not leave people to think that we are dealing with their concerns in a cavalier way.

I believe that biotechnology will become increasingly important in our lives. Molecular biology and genetics will come to dominate all of the life sciences and their applications to medicine, agriculture and the environmental sciences. We need to ensure that the UK has a share of research, development and production in this field. We could potentially provide the best opportunity for this field in Europe but we need not only have a sensible regulatory environment but enough investment to recover and enhance the research base in this field to provide innovative ideas, technology development and the trained, skilled manpower required.

Letter to the Clerk from The Brewers' Society (R W Simpson, Director)

Further to our letter of 25 February 1993, we are grateful for the opportunity to submit evidence to the Sub-Committee.

The following are our responses to the specific questions attached to your letter of 19 February:

(1) The brewing industry is very much biotechnology-based. Indeed, it is arguably the original biotechnology if the term is applied in its widest sense as meaning the application of biological systems to industrial processes. However, we assume that the Sub-Committee's interest is focused on genetic manipulation. The use of this new technology is important to the brewing industry. Our interest centres on the modification of brewing yeasts to improve the efficiency of the process and develop novel products. There is also potential for developing new varieties of barley and hops with improved brewing qualities within a shorter timeframe than traditional breeding programmes.

(2) The development of new yeast strains and innovative fermentation technologies will enhance the quality of traditional products, make them more economical to produce and open possibilities for new types of products that could not be produced by any other means. The application of biotechnology to crop development offers the opportunity to produce varieties with pest resistance, high yield and desirable quality characteristics. This would result in a reduction in the use of agricultural chemicals which would have cost and environmental benefits.

(3) The application of recombinant DNA technology to modify the properties and behaviour of brewing yeasts opens a wide range of opportunities. Past efforts to improve yeast strains using traditional selective techniques have had some successes, but these are limited by the "hit or miss" nature of the old technology. Genetic manipulation offers the opportunity to alter the yeast genome in a defined and controlled manner. This permits specific changes in the strain character without introducing undesirable characteristics. Better controlled yeast behaviour offers advantages in improved process control and thus cost savings. Product quality can be made more consistent and of a higher standard with advantage to the consumer. There are opportunities for eliminating or reducing additives by achieving the desired technological effect with the yeast itself.

One example of biotechnological techniques being applied to raw material improvements is the identification and elimination of viroids from hops. These have a serious deleterious effect on hop yield and alpha-acid content. Uninfected plants of the large majority of hop varieties grown in England have been obtained and potential sources of clean plants for the other varieties have been identified.

(4) Since biotechnology provides the possibility of developing new and novel products, the safety of those products must be considered. However, the risks involved are no greater than those associated with traditional methods of developing new products. Indeed, the use of genetic manipulation makes defining and understanding the novelty of the new product considerably more predictable. It is important that irrational fears should not impede the application of bio-technologies and the advantages that they confer when they do so in a manner that is more definable.

In most examples of genetic manipulation, the alteration to the organism is designed to confer improvements in its technological properties. Such organisms have often been developed to function well under strictly controlled technological conditions through characteristics that do not confer an advantage in an open environment. As an example, traditional brewing yeasts perform in brewery fermenters where they are not in competition with other organisms. They are not encountered in nature, presumably because they cannot compete. This is equally true of the genetically manipulated variants of traditional technological organisms. The introduced activity will not confer an advantage, indeed it is very likely that it will actually confer a disadvantage under the competitive conditions that occur in nature.

Genetic manipulation of traditional technological organisms is thus seen as a safe technology.

(5) For the reasons outlined above, we do not consider that the use of recombinant DNA technology in brewing introduces safety problems and would therefore wish to see any regulation that is deemed necessary, to be applied through a regime specific to the brewing industry.

We believe that the assessment of new production processes should fall within the remit of the MAFF Advisory Committee on Novel Foods and Processes.

(6) It follows that the Industry would wish to see vertical regulation, the characteristics of the product should be judged by its characteristics and not through the process by which it has been derived. The latter course is likely to promote subjective and irrational fears surrounding the use of genetic manipulation and this could form a significant barrier to its full exploitation.

(7) European legislation on biotechnology is based on a horizontal approach. For the reasons stated above, we believe that it is essential to move to a vertical approach as rapidly as possible.

(8) The USA is moving towards substantial de-regulation of biotechnology. In Europe, there is a more restrictive attitude, with variation across the Community. It is now recognised that over-regulation in some countries has had damaging effects. In Denmark research on plant genetics has been slowed down and in Germany many manufacturers are moving research on genetics out of German territory.

The UK implemented closed voluntary regulation of genetics research at an early stage and has now moved towards incorporating voluntary procedures into legislation. Industry in the UK has been fairly compliant to these trends and, for example, an expert group on ethical concerns of genetically modified foods has been convened recently. This approach, whilst being fairly stringent, seems to have caused minimum concern to the interested parties.

(9) The competitiveness of a bio-technologically based industry in any one country will be correlated with the extent to which the regulatory regime is perceived as reasonable or excessive. There is evidence of research by multi-national companies having moved from Europe to the USA to avoid over-rigorous regulations. The extent of research and scope in the UK indicates that it has not been significantly damaged by legislation.

However, within the brewing industry we are aware of some retrenchment as a result of a cumulative adverse public image of genetic manipulation. Such concerns are considered very seriously with strongly branded food and drink products where the investment in marketing could be damaged by adverse public reaction to the use of technology. This emphasises the importance of ensuring that regulation meets public concerns without aggravating and inflaming imaginary fears.

Products which are the result of genetic technology are already on the market and generally have created little controversy. However, the extension of the technology to food products that include intact genetically modified micro-organisms may raise a greater level of concern. Again, regulations should meet and alay rather than stimulate such concerns.

(10) There is a risk that the very high profile conferred on the products of genetic manipulation by regulatory requirements such as the need to advertise so called "deliberate release" may present problems of public acceptability. No manufacturer will wish to use a technology that is seen to be threatening by the public. It is essential that these fears are confronted and dealt with through a degree of regulation no more than is appropriate. Over-regulation will sustain suspicion and the UK could lose competitive advantage.

There is particular concern that unnecessary labelling of products derived from gene technology will erect a significant barrier to consumer acceptance.

(11) Although biotechnology improves industrial profitability, this must not be seen as the prime objective. As mentioned above, the use of genetic manipulation will result in distinct benefits to the consumer in terms of novel products and improved quality whilst reducing the environmental impact of the production process. As well as being made aware of these advantages, the public must be reasssured that bio-technologists are keenly aware of the concerns and any potential risks. Bio-technologists and the industries due to benefit from their activities, should recognise a responsibility for educating public opinion on these issues. Informed opinion and open debate can promote the required acceptance but require honesty and the greatest practicable openness from Government and Industry. Unfortunately, the proposal for regulating the use of genetically modified organisms and for the labelling of foods produced with them is likely to heighten consumer concerns.

(12) Centres of academic expertise will be important in generating the flow of innovative ideas that can be taken up by industry. Investment in this essential research should not be regarded as a luxury but as a necessity for maintaining the competitiveness of bio-technologically-based industries.

Evidence from the British Biotechnology Group plc

SUMMARY

- British Bio-technology is one of the largest and best capitalised biotechnology companies in Europe.
- Pharmaceuticals is Britain's most successful industry. Biotechnology will dominate the development of new drugs in the 1990's.
- The UK biotechnology industry lags far behing the US biotechnology industry.
- Future growth in biotechnology will be around 30 per cent per annum. Biotechnology is therefore very important for the UK.
- Biotechnology should not be regulated by an industry specific regime. Products should be regulated by the appropriate regulatory body.
- Vertical regulation should be adopted for biotechnology products.
- Despite efforts at regulatory harmonisation between MCA (UK), CPMP (Europe), FDA (US) and Koseisho (Japan), variations exist in interpretation. These differences should be minimised.
- Overregulation of biotechnology in the UK will have significant effects of research, product development, location and marketing and sales.
- Efforts to improve approval times by the MCA should be encouraged, as well as a more positive role by the MCA in facilitating compliance with the regulations.
- Improved education in schools is needed to promote a more positive public perception of biotechnology.
- UK financing of biotechnology is limited by lack of a public sector and moves to improve this situation through various tax incentives are needed.
- A scheme to bring forward the timing of tax credits for accumulated losses through investment in research and development to the year of incurred loss would be of great benefit.
- Efforts to speed-up the process of worldwide patent harmonisation are needed.
- Greater support should be given to the research base in Universities.

INTRODUCTION

Although biotechnology has a diverse and broad range of applications including human and veterinary healthcare, diagnostics, agriculture, foods and environmental products, the focus of this response will be on biotechnology and human healthcare. Consequently, issues relating to the release of GMOs (genetically modified organisms) and the regulations as laid out will not be considered in any detail, except in instances where reference to the regulations may facilitate an understanding of the issues surrounding UK, European and global harmonisation.

1. British Bio-technology Group plc

British Bio-technology is a leading U.K. research and development company in pharmaceuticals. Founded in 1986, the company is now one of the largest and best capitalised biotechnology businesses in Europe and the only biotechnology company to have its shares listed on the London Stock Exchange and NASDAQ in the US. The Company currently has four proprietary products in human clinical trials, three of which are currently progressing through Phase II testing, and all of which are aimed at substantial pharmaceutical markets.

British Bio-technology uses molecular biology and genetic engineering to develop highly innovative and proprietary pharmaceutical products. The Company's most advanced product is an immunotherapeutic vaccine for the treatment of AIDS and HIV, p24–VLP, which is based on an entirely new concept in the design of genetically engineered vaccines for the treatment and prevention of viral diseases and cancer. The Company has other programmes in cancer and cardiovascular diseases which utilise recombinant DNA technologies.

Through one of its subsidiaries, British Bio-technology Products Ltd, British Bio-technology provides high quality reagents and assays for medical and clinical research. Many of these products are used in molecular and cell biology.

2. The Importance of Biotechnology to UK Industry?

— Pharmaceuticals is now Britain's most successful industry, UK exports of pharmaceuticals are second only to aerospace products. In capitalisation terms several of Britain's largest companies are in this sector. A disproportionately high number of the world's best selling drugs are UK products.

In 1991 the pharmaceutical industry had a worldwide market of $194.7 billion, predominantly split between Europe, North America and Japan, with 12.5 per cent growth over the previous year. The UK was the sixth largest market, with revenues of $6.072 billion, with growth of 11 per cent. Two of the top 10 worldwide companies, Glaxo (2nd) and SmithKline Beecham (8th) are British, with two other companies (Zeneca and Wellcome) in the top 30 (see Table 1 for a comparison of the US, Europe, UK and Japan). Within Europe Glaxo is the leading company.

TABLE 1

The Top Pharmaceutical and Biotechnology Companies and Products by Geographical Territory

	US	*Europe*	*UK*	*Japan*
Top 30 Pharmaceutical Companies	13	9	4	4
Top 15 Pharmaceutical Products	7	3	5	—
Top 15 Biotechnology Companies	14	—	1	—
Top 10 Biotechnology Products	10	—	—	—

In terms of products, five of the top 15 products are British—Glaxo's Zantac (No. 1), SmithKline Beechams' Tagamet (No. 5) and Augmentin (No. 13), Zeneca's Tenormin (No. 11) and Wellcome's Zovirax (No. 14). Together these products have a combined revenue of over $5 billion.

— It is likely that the biotechnology industry will dominate the development of new drugs in the 1990s and will ultimately change the landscape of medical practice by the year 2000. This could end the era of dominance by the major drug companies that have relied principally on traditional organic chemistry for drug development since the late 1940s. Whithin the next eight years biotechnology firms could replace several of the major drug companies as perceived leaders in the industry.

Currently, over 600 biotechnology products are in development, and in the US, the FDA expects 1,200 biotech products by the year 2000. Already one US company, Amgen, has joined the ranks of the major pharmaceuticals and is likely to be joined by others.

— The UK biotechnology industry lags far behind the US biotechnology industry.

In the US there ore over 500 biotechnology companies of which 350 are quoted publically. In the UK, a handful of biotechnology companies are established. They have the challenge of spearheading the emergence of UK biotechnology as a dominant force in the world. Last year British Bio-technology was the first biotechnology company to obtain a full listing on the London Stock Exchange. British Bio-technology and Cantab Pharmaceuticals are now quoted on the US over the counter exchange, NSADAQ. Several other emerging companies are likely to seek listings within the next two years.

Within the top 20 biotechnology companies worldwide (based on market capitalisation), only one is from the UK, British Bio-technology (No. 15). As yet, no sales have been recorded from biopharmaceutical products developed by UK companies, despite a substantial increase in product sales by US companies.

In financial terms, the US biotechnology industry (including healthcare, agriculture, diagnostics etc.) now generates revenues of $8.1 billion, an increase of 28 per cent over the previous year, and is set to increase substantially to $60 billion by the year 2000, so that high levels of growth will continue and will be significantly higher than most other industrial sectors. The UK market was estimated to be only £525 million in 1991 with an annual growth rate of 20–30 per cent.

— Biotechnology is likely to play a key role in the future development of the healthcare industry in industrialised countries and will be capable of generating considerable revenues in Europe, the US and Japan and will be less susceptible to generic drug competition. These companies will be likely to sustain earnings growth of 20 per cent p.a. or more compared with major drug companies (10–15 per cent estimated earnings growth).

There are a number of reasons for this growth potential.

1. Biotechnology drugs (Epogen, Neupogen, Ceredase, Intron A and Leukine) are unique and represent a highly orignal form of therapy. They represent the first generation of drugs of their class.

2. It would be difficult to make a generic copy of any of these compounds because of (i) the high capital costs of building a mammalian, bacterial or yeast cell fermentation facility (a $70–100 million investment); (ii) the need for a highly skilled labour force; (iii) most of the patented biotechnology products have patents that extend into the 21 Century.

3. Biotechnology products have been shown to save the healthcare system money because of their efficient biological actions. For example, the growth factors reduce costs by reducing infection in cancer patients, thereby eliminating or reducing in-patient hospital stays and antibiotic use. These drugs also allow for increased chemotherapy dosing and thereby increase the chances for partial or complete remission in cancer patients.

4. Biotechnology products, being highly potent, have higher gross margins than traditional synthetic drugs and therefore allow for greater pricing flexibility.

5. Current prices for most of the biotech compounds now on the market are well within acceptable therapy costs.

6. There drugs have been shown to improve the quality of life of patients, thereby returning the patients to work and assisting in making the patient productive again in his or her job.

The overall effect of these factors will be a high level of sustained growth which to date has been approaching 30 per cent per annum.

— The rate of scientific discovery with biotechnology will continue to fuel high growth. Genetic engineering is advancing medical science at a far greater pace than most scientists throught possible only a few years ago. Consequently, new technologies being developed due to biotechnology could have a dramatic effect on medical practice.

Discoveries are now made on a weekly basis. Singnificant advances are being made in new treatments for allergies, cancer, heart disease, infectious diseases, and diseases of the nervous system. Techniques such as genetic therapy are entering clinical practice and offer the hope of reducing the use of toxic chemotherapeutic drugs and perhaps curing disease. At least 18 gene replacement trials are in progress in diseases ranging from brain cancer to AIDS.

Over 20 biotechnology firms are now engaged in some form of gene therapy research. Likewise the human genome project is beginning to bear fruit and the first physical map of two human chromosomes (the Y chromosome and chromosome 21) have been completed. We expect that over the next decade tremendous knowledge will be gained in understanding disease, as the human genome (23 pairs of chromosomes, 100,000 genes, three billion bases) is deciphered, which ultimately should lead to more advanced genetic therapy.

Biotechnology will also impact rational drug design. The overuse of antibiotics over the last 20 years has led to a dramatic increase in multi-resistant bacteria. Additionally, the increase in AIDS has led to a very serious rise in the incidence of tuberculosis and many of these new cases are resistant to standard drug therapy. Drug resistance can add substantially to medical bills. There are now 10 major bacterial groups that have exhibited strong anti-microbial resistance and clinicians and scientists believe that the development of new drugs to overcome this resistance is through rational drug design. The future of medicine almost certainly belongs to biotechnology.

If this sounds far fetched, there is ample precedent for new technologies revamping industry sectors. It is not much more than 10 years ago Steve Jobs invented the personal computer and Apple, Compaq, and Sun Microsystems displaced IBM, DEC and Wang as industry leaders. Likewise the discovery by Cohen & Boyer in the early 1970s that DNA could be transferred between organisms of different species through genetic engineering ushered in a new age in medicine. It is a discovery that the major pharmaceutical companies have been slow to act upon.

— Healthcare and biotechnology will be greatly influenced by demographics. In Europe, Japan and the US the populations are ageing.

Age ultimately brings illness, disease and death. The healthcare needs of the UK and other countries, particularly the US will increase dramatically in the next 10 years. Heart disease and cancer are likely to remain leading causes of death. Consequently, technologies which increase effectiveness of treatment and have benefits on health economics are likely to be increasingly important in the future. For example, the growth factors are having an overall benefit to healthcare costs.

— Biotechnology is therefore very important for the UK. It is one of the few, if not the only, industry sector which has the potential to sustain high growth and significantly contribute to wealth creation.

3. THE FUTURE PROSPECTS AND OPPORTUNITIES FOR UK BIOTECHNOLOGY

The future prospects and opportunities for the technology are varied and substantial. In the area of healthcare alone, the technology has led to an increasing number of new products being brought to the market—see Table 2. Epogen represents the most successful first-year launch of any biotechnology product and the second most successful pharmaceutical launch in US history with first year sales of $300 million.

TABLE 2

Approved Biopharmaceutical Products

(as approved by the US Food and Drug Administration)

1. Erythropoietin (Epogen–Amgen) for the treatment of anaemia associated with kidney dialysis

2. Gamma interferon (Actimmune–Genentech) for the treatment of chronic granulamotous disease

3. Granulocyte colony stimulating factor or G–CSF (Neupogen–Amgen) as an adjunct to chemotherapy

4. Granulocyte macrophage colony stimulating factor or GM-CSF (Leukine-Immunex) for bone marrow transplants

5. Hepatitis B (Engerix–SmithKline Beecham; Recombivax HB–Merck) vaccine for the prevention of hepatitis B

6. Human growth hormone or hGH (Protopin–Genentech; Humatrope–Eli Lilly) for the treatment of pituitary dwarfism

7. Interferon-alpha2a (Roferon-A–Genentech/Hoffman-La Roche) for hairy cell leukaemia and AIDS-related Kaposi's sarcoma

8. Interferon-alpha2b (Intron A–Biogen/Schering-Plough) for the treatment of hairy cell leukaemia, genital warts and AIDS-related Kaposi's sarcoma

9. Interleukin-2 (Proleukin–Chiron) for the treatment of renal carcinoma

10. Muromanab CD3 (Orthoclone OKT3–Ortho Pharmaceutical) for kidney transplant rejection

11. Tissue plasminogen activator or tPA (Activase–Genentech) for the treatment of myocardial infarction and pulmonary embolism

Within the UK, biotechnology products are under development for a wide range of disorders and offer significant opportunites for treating diseases and disorders which previously have been untreatable through more conventional routes. Table 3 shows a selection of drugs under development by UK biotechnology companies. Each of the areas of focus represent substantial markets. For example, the worldwide cancer market is valued at over $5 billion, sales of thrombolytic agents were over $700 million worldwide in 1991, an AIDS vaccine is likely to have a market between $1 and $2 billion, and the market for sepsis is projected to be $500 million. These are substantial markets which are likely to be increased as new technologies and products are developed.

4. THE ROLE OF REGULATION IN BIOTECHNOLOGY

— Biotechnology regulations come under HSE regulations. These regulations address the containment of Genetically Manipulated Organisms (GMOs) through careful monitoring of the processes involved, adequate health monitoring for staff and demonstrating the appropriate levels of equipment and process containment.

These regulations cover all aspects relating to safety and experience in the use of GMOs over the last 15 years has demonstrated that adequate regulations are in place. Additional regulations would place too great a burden on the industry.

— Biotechnology should not be regulated by an industry specific regime. Since it is the products which require regulation, then these should be regulated by the appropriate regulatory body.

A further issue is the major discrepancy between the regulation of "natural" biological products and those which are derived from genetic manipulated organisms. A classic example is the production of recombinant interferon, where the products are placed under strict regulation with both in-process and final product monitoring and a limit on the quantity of DNA present of less than 100 pg (10^{-12}gms) per dose. However in order to stabilise the interferon, non-recombinant human serum albumin is added, which itself contains DNA of human origin, often resulting in an excess of 1μg in the final product. Some rationalisation is required to bring recombinant and non-recombinant processes into line in order to allow biotechnology to compete successfully with conventional technologies.

— Vertical regulation should be adopted for biotechnology products. Horizontal regulation (where it is in operation) should evolve into vertical regulation.

In the past, horizontal regulation was justifiable when methods were unavailable or inadequate to characterise fully the end product. Then greater emphasis was placed on the methods of production and the quality control checks performed during the production process to understand the nature and quality of the end product. Methods are now available which permit the end product to be fully characterised. If it can be shown that the end product is what it should be, that it is safe, particularly with regard to impurity, and of a satisfactory quality for the intended purpose, then the process by which it is obtained is not so important. Given this, there should be a shift in emphasis away from the need for extensive detailed information on the process by which the product was produced to focusing on end product characterisation. In summary, emphasis should be placed on vertical regulation as it is the product and not the process which is administered.

[NOTE: "Vertical" regulation is taken to mean product-driven regulation, while "horizontal" regulation is defined as process-driven regulation.]

5. COMPARISON OF CURRENT REGULATIONS WITH COMPETITOR COUNTRIES

- While the international regulatory goal is the maintenance of common standards and attitudes without the issuance of formal inflexible regulations, some variation does arise between different countries. There is not much significant difference between the regulations and guidelines set out for the EC CPMP and US FDA, although there are differences in interpretation. Similar variation in interpretation exists between the UK MCA and CPMP and moves should be made to eradicate this.

Figure 1 compares the competitive differences between EC member states and between the EC, US and Japan in terms of legal requirements and additional investments for safety measures. The US, Japan and UK are grouped together with medium to high legal requirements and low additional investments. Not surprisingly Germany and Denmark come out the worst.

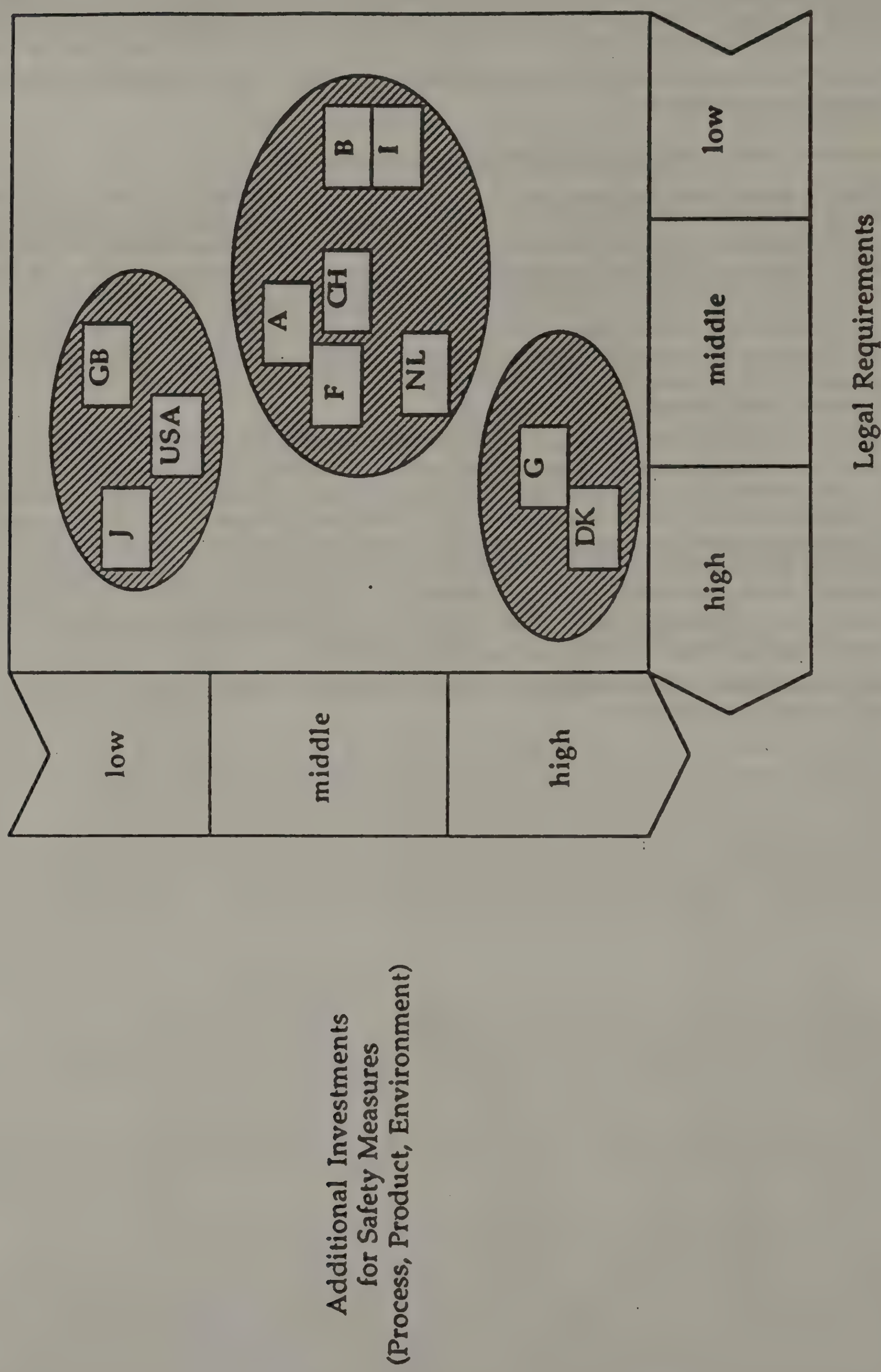
Both the FDA and CPMP emphasise the need for flexibility in approach with regard to data requirements for individual rDNA products rather than hard and fast rules and regulations. It could be said that the EC is a little more regimented and rigid than the FDA in its approach in that it has issued guidelines whereas the FDA take a "recommendation" approach with the "Points to Consider" documents. All regulatory agencies say that the requirements have to be considered carefully in relation to the product in question, on a case-by-case approach. This flexible approach should be encouraged—we wish to avoid the introduction of hard and fast rules. However, the impetus and input for case-by-case approach should be *a priori* and not *a posteriori*.

- Overregulation of biotechonology in the UK will have significant effects on research, product development, investment, location and marketing and sales.

If an imbalance between the UK regulatory environment and other competitor countries arises, then this will have ramifications in several areas:

FIGURE 1

Competitive Differences between EEC Member States and between EEC, US and Japan



- Research: enhance the "brain drain" since the climate will be unsuitable for innovative research in biotechnology.
- Product Development: increased regulation will increase the costs of product development, reducing the ability of entrepreneurial companies to compete effectively.
- Investment: overregulation will reduce investment in biotechnology.
- Sales and Marketing: any increase in regulation will delay product launches, thereby increasing the cost of development. This will either lead to an increase in drug prices or reduce the level of investment in research and development.
- Location: Many US companies have set up subsidiaries in Holland, rather than in the UK. The regulatory climate in the UK is quoted as one of the reasons for this choice. If the UK is to lead Europe in biotechnology, this process must be reversed. An unfavourable regulatory climate would also lead to major pharmaceutical companies establishing manufacturing facilities elsewhere.

For example, when BASF decided to transfer its oncology and immunology research to the United States, it sent shock waves through the rest of West German industry—and raised fears among other European companies that environmental and safety pressures might conceivably make some parts of Europe no-go areas for genetic engineering. Clearly such a situation in the UK would be most damaging for biotechnology.

However, Germany's Genetic Engineering Act, introduced in 1990, has already helped some German companies to win approval for new biotechnology facilities. In October 1990, for example, Hoechst—after a six year battle—was given permission to operate a pilot-scale insulin production plant, despite the fact that it would use genetically engineered *E. coli* microorganisms. BASF has won approval for rTNF at its Ludwigshafen site.

- It is essential that the open and constructive dialogue which already exists between industry and the regulators, be allowed to continue. Industry must be allowed to input and comment on draft guidelines, regulations etc. prior to implementation.

It is also vital that the flexible approach with regard to the applicability of the requirements/guidelines be maintained and that each product continues to be judged on a case-by-case basis. The question of consistency in interpretation needs to be carefully considered. The developing global markets must not be hindered by diverse rules or basically comparable rules which however still allow different interpretations. Above all we wish to avoid the introduction of hard and fast rules by the regulators concerning the regulatory requirements for biotechnology products.

- Although the FDA is looking to improve timescales for product approvals by receiving additional funding from industry, in the UK there appears to be little emphasis on speeding up the rate of product approvals.

The speed of product approvals could be improved, since any delays will either increase drug prices or reduce the level of reinvestment in research and development.

- The MCA should be encouraged to take a more positive and proactive role in the product approval process for licensing biotechnology products.

For example, the National Institute of Biological Standards and Control could actively assist and encourage companies during preclinical and clinical testing and facilitate the regulatory process, in consultation with the MCA.

- There is a danger that increased regulation by the EC will reduce the UK's competitiveness with the rest of the world.

Biotechnology is now very much on the European Community agenda. In mid-1991, no fewer than six Directives relating to biotechnology had already been approved, five more were waiting ratification and another eight were in draft stage. There is a danger that excessive regulation from Europe will stifle the UK's emergent biotechnology industry. Unfortunately, it is often those countries, such as Germany and Denmark, where the biotechnology industry is the least developed, which have lobbied hardest for additional regulations. Indeed, there is an increasing trend in regulations in Europe and UK, with a decrease in the USA. The UK probably has the most developed biotechnology industry in Europe and so should be driving or influencing any EC initiatives with the aim of promoting biotechnology, rather than reacting to EC legislation.

If additional regulations are imposed then the exploitation of research conducted in the UK will be prevented. The situation in Germany has shown how damaging attitudes can be to the industrial exploitation of biotechnology where several companies have been forced to establish manufacturing facilities elsewhere. In the UK, where there have been concerns over the "brain drain" from Universities and Research Institutes, if an antagonistic regulatory environment is set up, then not only will our technological base be exploited elsewhere, but also investment in an area which has excellent growth potential will disappear.

- The UK should take an active, leading role in determining the European Regulatory framework. For example, the UK should lobby for the establishment of the European medicines Agency to be set up in the UK.

6. Issues of Public Acceptance

- unfortunately for biotechnologists, the public trusts environmentalists more than it trusts the industry. Effective ways of addressing this problem are needed since public perception could effect the regulatory framework. There is evidence that this is already happening in the emergence of a new range of social and ethical issues. Altough many biotechnologists welcome sensible regulation, there has been concern about the prospect of the "Fourth Hurdle"—with soci-economic need being added to the traditional considerations of safety, quality and efficacy.

In Europe, as compared to the US and Japan, the questions on safety and potential environmental danger through production plants or even scientific laboratories is of importance in the public opinion, eg Germany and Switzerland. Surprisingly, safety of a recombinant drug itself does not play essential role. Consequently the attractiveness of a plant location or research centre is influenced by the duration and the conditions of the approval procedures with legal possibilities of the public to interact. One simple reason for these differences is the lack of information given to the public, thus opening the door to emotional discussions of the safety issue in biotechnology.

- Issues of Public Acceptance should be addressed through improved education in our schools and higher education centres and the direct targeting of public perception issues as and when they arise.

For example, in the past efforts have been made by the Government to introduce computers into schools, more effective ways of promoting and explaining biotechnology in our schools should be followed.

7. Other Factors which Play a Crucial Role in the Competitiveness of the UK Biotechnology Industry

There are several additional areas which will be crucial in the competitiveness of the UK biotechnology industry.

(a) *Financing of UK biotechnology companies*

- The financing of UK biotechnology companies has always been difficult and is constrained by the lack of public sector companies. British Bio-technology has pioneered the way for high technology companies to be listed on the London Stock Exchange.

The financing of biotechnology companies in the UK lags far behind the US. There remains a lack of high risk capital in the UK and moves should be made to improve this situation.

- Tax incentives for biotechnology companies should be set up to encourage high risk investment in the biotechnology sectors. These incentives, such as positive tax credits, should promote long term high risk investment commensurate with the long timescales (up to 10 years) for product development.

Many other countries give tax incentives for investment in research and development, or write-offs against capital gains tax for investment in biotechnology companies.

An approach which is becoming more widely used is the use of positive tax credits. Instead of accumulating losses over a period of years which are then offset against future profits, and hence taxes, a much more beneficial approach would be to receive credits against the losses in the year that they are incurred. Consequently, the Government would reimburse a company which funded an agreed programme of research and development in the year it arose. Credit against future corporation tax would no longer be carried forward and the company would benefit at a time when it most needed financial support.

The Government and local authorities could also take a more encouraging role, such as in providing capital grants for establishing manufacturing plants, or in giving special tax incentives to company's that manufacture in the UK.

(b) *Intellectual Property and Patents*

- The ongoing problems over biotechnology patents and their interpretation is a critical area for the future competitiveness of the UK biotechnology industry. As the biotechnology industry has evolved, one of the key areas needed for its success is good patent protection.

Difficulties have been encountered in interpreting biotechnology patents within the existing framework of patent law, which has led to unevenness in the scope of granted claims for many inventions. The major area for comparison has been in chemical patents where there is now a substantial body of case law which defines the scope of claims in relation to exemplification and the prior art, and where a sound understanding of the structural and functional interrelationships is available. Such a corpus of knowledge does not exist in biotechnology yet, and it is likely to be some time before such a knowledge base exists. There remains no clear understanding of structure and function and of issues surrounding novelty of gene sequences for known proteins.

- Substantial differences exist in the patent laws of Europe, the US and Japan.

For example in the US, the priority date of a patent is based on a first to invent, rather than first to file system. Even in Europe there are differences in interpretation of patent law between Europe and the UK. A recent example was the Genentech tPA case where, in the UK the patent was revoked after an action by Wellcome, whereas in Europe, a recent opposition upheld the Genetech patent.

Problems in different national requirements for patents and their impact on competitiveness has been highlighted by the US National Institutes of Health (NIH) application for 2,000 novel gene sequences with no known function. Such genes or fragments have been identified by cDNA sequencing rather than genomic sequencing and the only utility disclosed in the application was that the genes or gene fragments could be used as probes. The application has been rejected by the US Patent and Trademarks Office on the basis of lack of novelty, although the NIH now have permission to file a response. There are concerns that the NIH's behaviour is an indicator of increasing US protectionism in biotechnology. In contrast, in Europe, the European Patent Office last year informed the French minister that it would not grant such an application.

The EC is currently drafting a Directive on the Protection of Biological Inventions. Issues concerning the patenting of lifeforms, such as the "Harvard Oncomouse" and farmer's privileges are addressed. It is questionable whether the EC needed to draw up such a Directive; and only serves to add another layer of complexity to an already complex situation. What is clear is that European patent law, particularly in relation to the scope of patentable subject matter, will have to track developments in the US if it is to remain competitive, especially in areas such as the patentability of lifeforms.

- For the UK to be competitive, moves towards improved harmonisation of patents are needed. Parallel track negotiations are underway through the United Nations' World Intellectual Property Organisation (WIPO) and General Agreements on Tariff and Trade (GATT). The slow rate of progress in these negotiations is disturbing and efforts should be made to speed up the process. It does appear that the US will be moving to a first to file system in 1994, but it is likely that concessions will have to be made in Europe in return.

There clearly remains much uncertainty within the field of biotechnology patents, and while parts of this uncertainty will be clarified in the Courts, it is important that harmonization of patent law on a worldwide basis is pursued vigorously.

(c) *Other Issues*

In addition to support for financing high technology and promoting the increased education and awareness of the benefits of biotechnology, other areas where additional support could be made by the Government include:

- Supporting research in our Universities
- The increased identification of a Government Department to champion biotechnology. The obvious choice for this is the Department of Trade and Industry.

In conclusion, any incentives set up by the Government for biotechnology and high technology industries aimed at promoting the competitiveness of the UK are to be welcomed.

Evidence from The British Society of Plant Breeders Ltd

1. *What is your interest in biotechnology?*

The British Society of Plant Breeders represents the interests of the majority of UK plant breeding companies and as such is concerned with all legal and regulatory issues relating to the application of biotechnology to plants.

The plant breeding industry has traditionally been based upon techniques of cross pollination followed by often imprecise selection techniques to produce varieties of improved plants. Tissue culture techniques have been used to a limited extent for multiplication of plant material.

New developments in molecular biology give the potential to use much more precise analytical techniques (eg RFLPs) to assist selection of improved plants. These analytical methods will also facilitate the selection of material for gene banks. Genetic transformation permits the use of genes from unrelated species in order to improve pest, disease and quality characters in ways which are not possible using conventional crossing techniques.

2. *How and why is biotechnology important to UK industry?*

The UK has a strong academic and industrial research base in plant biotechnology which should be exploited. There is considerable benefit from basic research in molecular biology which is particularly strong in the UK. The "spin off" from molecular biology in medical research is significant.

The public stand to gain from wider choice of safe food which is produced in a way which results in environmental benefits (eg less use of farm chemicals). Farmers will gain from having a wider range of crop options, some of which will require less inputs.

Failure to exploit the technology may leave the UK without the environmental benefits and more dependent on imported agricultural and food products.

3. *What future prospects and opportunities does the technology offer?*

The impact on crops could be considerable. The two main opportunities are plant varieties which can perform adequately with reduced chemical inputs (eg plants with improved resistance to pests and diseases) and modified crops from which new or improved products can be derived.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

In the context of plants the issues are: safety to workers; safety to users and to consumers; and negative impact on the environment. These are all addressed by regulation which is in place or which is pending. Although these possible areas of risk are unlikely to be significant for plants industry accepts that regulation is necessary and that safety must be established on the basis of proven experience if the public is to be convinced.

The present system of Advisory Committees eg ACRE and ACGM is beneficial.

5. *Should biotechnology be regulated by an industry specific regime?*

Yes. Biotechnology is not an industry and its applicaton will occur in defined and unrelated sectors of business eg pharmaceuticals, agriculture, brewing, etc. It therefore makes sense to have a sectorial approach for operational reasons. Clearly there must be no conflict between the regulations for the various sectors.

New plant varieties (however produced) must undergo statutory testing before they can be marketed. This needs to be integrated with regulations to market genetically modified plants. Industry must have the option to have all clearance procedures run in parallel. If there is not an industry specific regime industry may face unnecessary costs and delays in obtaining clearance.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better then a vertical regulation (where a product is judged by its characteristics)?*

Definitely not. In general, the safety of a product is a property of that product rather than of the process by which it is made. A single product made by two distinct methods, one biotechnological the other not, cannot have two different levels of safety. The method of production may have a bearing on the safety to manufacturing workers and it may affect by-products but not the safety of the product *per se*.

A further reason for the vertical approach is that the regulations must be scientifically sound and must recognise the biological differences between viruses, bacteria, plants and animals. One of the basic difficulties with the present EC Directive on "Contained use" and "Deliberate Release" of Genetically Modified Organisms is that these crucial biological differences are not adequately recognised because of the attempt to force everything into a single system originally designed to deal with microorganisms. At the very least the crucial differences need to be recognised.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

Yes, but only as a second best alternative to having effective sectorial regulations in the first place.

8. *How do current regulations compare with those of competitor countries?*

The UK is "middle of the road" with respect to the rest of the EC. The EC is perceived as having a bureaucratic approach which places insufficient importance on scientific principles and which pays little regard to the needs of industry. The approach of the US authorities in contrast is pragmatic, does take account of the science, and makes use of existing (sectorial) regulations. The plant breeding industry prefers the US approach. However both the US and the EC regulations are still evolving.

The implementation of the EC Directives relating to "Contained Use" and "Deliberate Release" of Genetically Modified Organisms into UK law have led to positive interaction between the UK authorities and the plant breeding industry. The British Society of Plant Breeders accepts that UK authorities are striving to ensure UK breeders are not placed at a disadvantage. A "level playing field" is essential.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards*

1. *research*
2. *product development*
3. *investment*
4. *location*
5. *sales and marketing?*

At best neutral on all aspects.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

It is unlikely to prevent exploitation. Given the comparative ease of relocating scientific research it is important to ensure that UK companies are not given any cause to move abroad.

11. *How best can issues of public acceptance be addressed?*

This is a major issue. Public perception of the risks involved in the technology could be a major obstacle to the development of biotechnology. Therefore there is a need for a concerted campaign to inform the public what the benefits and risks are. To be effective the information must be seen to be completely unbiased. The British Society of Plant Breeders is exploring ways in which it can collaborate with interested parties to bring about informed debate.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

— Unreasonable cost of compliance with the regulations.

The current draft of the EC directive on patenting of biotechnological inventions has an amendment, supported by a large majority in the European Parliament, which states that farmers will have the right to save seed of patented material with no payment of a royalty. Such an exemption has no precedent in patent law and is a serious disincentive to investment by plant breeding companies. The problem of farm saved seed must be solved.

— The imposition of compulsory licences which is another feature of the Directive on patenting of biotechnological inventions is also unwelcome. Industry accepts the grant of a compulsory licence only when in the public interest.

— Unreasonable food labelling requirements for products involving genetically modified organisms.

Evidence from British Sugar Beet Seed Producers Association (R E Pritt Esq, Chairman)

1. *What is your interest in biotechnology?*

Biotechnology brings a series of new tools which can be used by plant breeding companies to speed up product development and to combine quality characters that have so far been impossible to combine. Plant breeding companies will need to further develop and utilize the array of techniques brought about by biotechnology in order to meet the demand for the "products of tomorrow".

2. *How and why is biotechnology important to UK industry?*

Biotechnology will enhance the competitiveness of UK plant breeding and agricultural industries making the UK less reliant on imported agricultural and food products. It will provide solutions to previously intransigent problems. There should be a wider choice of crop options and "safe" food, produced in environmentally friendly conditions (eg, less use of chemicals).

3. *What future prospects and opportunities does the technology offer?*

The technology will offer new solutions for crop management, resistance to disease and pests, quality improvements and ecological friendliness.

4. *Which developments in biotechnology raise issues of safety and should they be addressed?*

Combining traits from incompatible organisms have raised issues of safety and so have other techniques in the framework of biotechnology.

All safety issues should be dealt with through appropriate legislation executed in a harmonized way by the member states of the European Community. Present experience would suggest that there should be no major safety concerns for plants. It is important, however, that the public is convinced of this.

5. *Should biotechnology be regulated by an industry specific regime?*

Yes—If "industry specific" refers to Agriculture as a whole, then it would be most efficacious to separate the regulation of plants and their products from animals and from micro-organisms which involve very different risks and ethical concerns. New plant varieties must undergo statutory testing before they can be marketed. This needs to be integrated with regulations to market genetically modified plants.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

No. Regulations would be based on resulting product rather than on the process by which the product is developed. A vertical legislation rather than a horizontal legislation is, therefore, the most appropriate approach. Horizontal should not be excluded however—novel processes may produce novel (and maybe unpredictable) risks.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

Although a balance between the two approaches is advisable evolution should be towards vertical regulation. This is likely to be more pragmatic and practical than horizontal regulation.

8. *How do current regulations compare with those of other competitor countries?*

In Europe, regulations are in development and recent initiatives have been taken in eg Belgium, France and the Netherlands.

In the USA, current regulation is more favourable for the application of biotechnology into agriculture than the present regulation in the UK.

In the Far East, primarily in Japan, regulations are being implemented comparable to those in the USA.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards:*

(1) *Research*
(2) *Product development*
(3) *Investment*
(4) *Location*
(5) *Sales and marketing?*

There is a tendency for biotechnology research, product development and investment to move from Europe to the USA. Sales and Marketing of products will, therefore, be subject to patents and licensing agreements from American companies. This poses a possible serious long term risk to UK industry competitiveness.

In general terms the regulatory regime does not provide any encouragement in any of these areas.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

No. The present situation will mean, however, that exploitation will be slower and less effectively applied than in the USA.

11. *How best can issues of public acceptance be addressed?*

Appropriate information to the public regarding the prudent use of biotechnology is critical. It is the responsibility of both governmental institutions and the private sector to make sure that the public receives appropriate and correct information about the potential benefits and the potential hazards with different applications of biotechnology. It is to be recommended that both governmental and private sectors address this issue of information in a co-ordinated way and in consensus. It is important to stress that in many cases we are substituting a form of biological control for the use of noxious chemicals. Products coming out of this new technology will be whole plants rather than something invisible so that you can at least see what is going on.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

(a) The requirements for and extent of labelling of transformed products could have a large influence.
(b) Product development using biotechnology is very complex and long term. Transparent, consistent regulation is essential to plan long-term investment.
(c) A sound academic base. Avoid the "brain drain".
(d) Keeping the costs of complying with the regulations at a reasonable level.

Evidence from Professor Derek C Burke, Vice-Chancellor of the University of East Anglia

Biotechnology is a pervasive, enabling technology with universal application. It has already delivered a range of new products and processes and will continue to do so. Specific targets have invariably been attained faster than expected, and this will continue to be true, since the technology base is still envolving rapidly. It is applicable to a wide range of chemical, pharmaceutical, agricultrural, health care and food industries, and it is essential for the continuing development of UK competitiveness in all these areas.

The most serious impediment to its successful widespread use is inappropriate regulation. Regulatory processses have already been established to satisfactorily protect the laboratory and process worker, and they are rapidly being developed to protect the environment. Appropriate consumer protection is however, still developing. This situation is satisfactory in the pharmaceutical area, where the risk/benefit analysis is advantageous for the consumer, but less so in food and agriculture. Unless handled well consumer resistance could seriously handicap application of biotechnology to those latter industries.

I argue for regulation that is largely driven by the nature of the product, but with great sensitivity shown to the novelty of process involved. The key, however, I believe to be openness of procedure, where much still remains to be done.

1. (a) I have personal experience of the laboratory techniques of biotechnology as leader of a research group at the University of Warwick, cloning the human interferon genes, and maing the first monoclonal antibody against interferon both in 1981. The former project was a collaboration with the Wellcome Foundation. The latter with Celltech Limited.

(b) From 1982–86 I was Scientific Director and Vice-President of Allelix Inc, Toronto, the largest Canadian biotechnology company. As such I was responsible for about 180 scientists working in several areas of biotechnology (plant cell transformation, gene expression, diagnostics) with the object of achieving commercial products.

(c) As Vice-Chancellor of the University of East Anglia since 1987, I am Chairman of the John Innes Council and a member of the Governing Bodies of the Associated Cambridge Laboratory and Sainsbury Laboratory. These three laboratories make up the John Innes Centre for Plant Science Research—the largest, and the best, group of plant biotechnologists in the UK. I am also a member of the Advisory Board for the Institute of Food Research.

(d) I am Chairman of the Advisory Committee on Novel Foods and Processes, which deals with all novel applications of biotechnology for the food industry. I am also a member of the Advisory Committee on Genetic Modification.

2. Biotechnology is:

(a) a universal discipline, providing new processes or products for use in all disciplines related to living cells;

(b) an enabling discipline, with the capability of affecting a very large number of processes, in ways not always possible to predict;

(c) a rapidly evolving discipline; from its origins in mid 1970s it has grown and diversified, invariably reaching specific targets sooner than predicted.

It is therefore important to:

(a) the pharmaceutical industry, with a number of new products now in the market place, such as interferon, growth hormone, modified penicillins;

(b) the chemical industry, since it can produce chemical intermediates, particularly chiral compounds, more cheaply than current processes, and also new products such as a biodegradable plastic;

(c) the agriculture industry, since new plant cultures offering resistance to pests are in sight, and other important modifications (sale, drought and temperature resistance) are achievable;

(d) the environmental industry, offering new methods for decontamination of water and land ("bioremodiation");

(e) the food industry—offering modified micro-organisms (eg yeasts and lactobacilli) with novel properties, methods for changing the composition (and hence dietary role) of fats, new methods for producing enzymes (chymosin for cheese ripening), or modified enzymes to make new products or conventional products more cheaply;

(f) the personal care/household products industry, offering improved enzymes for washing powders and enzymes for use in personal care (depilation);

(g) the law enforcement and legal profession by development of DNA finger-printing;

(h) the health care industry, with the development of many specific diagnostic reagents, for blood group typing, pathogen identification etc.

3. Very substantial opportunities, for example:

3.1. *Pharmaceutical Industry*

(a) development of potential anti cancer agents such as the interleukins and other proteins with cell-modifying properties;

(b) development of agents to modify cell proliferation in specialised systems, eg the haemopoectic system;

(c) gene therapy, selection and administration of genes responsible for inherited diseases;

3.2 *Food Industry*

(a) modification of fats to lower saturated fatty acid composition of diet;

(b) modification of yeasts to produce low calorie beers;

(c) modification of lactobacilli to produce organisms producing antibiotics to protect against food spoilage;

3.3 *Agricultural Industry*

(a) development of crop cultivars with desirable agronomic traits;

(b) development of crop cultivars for production of useful industrial chemicals to replace food crops;

3.4 *Chemical Industry*

(a) development of new methods for production of chiral compounds;

(b) development of enzyme catalysed processes to replace chemical processes.

These opportunities may be characterised as:

(a) existing products produced at lower cost (eg interferon);

(b) new improved products to replace existing products (enzyme in washing powders)

(c) products that improve health (gene-replacement, unsaturated fats);

(d) products that improve consumer choice (new flavours, spoilage resistant products).

These new products are most acceptable to the consumer in the health care services and health improvement areas; less so in the food and agriculture industries.

4. — Laboratory and production safety—now working well through the work of ACGM;

— Environmental safety—now controlled through the work of ACRE;

— Food Safety—the responsibility of ACNFP.

These committees are, I believe, handling the technical isues well. They are having to change quite rapidly to meet public acceptance issues (see 11), and it remains to be seen whether what they are doing will be adequate in scope and delivery.

5. The answer to this question depends on whether you regard biotechnology processes as different *in kind* from previously existing processes or not.

That decision in my view depends ultimately on whether or not moving genes across the species barriers observed in nature is judged to be so dangerous/unwise/improper that all products made by such processes require special treatment.

If, however, one concludes that safety considerations stem from the nature of the product, then the process, and specifically whether it involves trans-species gene transfer or not, is irrelevant. Then the safety is determined by the class of product—ie food, pharmaceutical etc.

My view is a modified version of the second attitude. Safety assessment starts with the product, then looks at any foreseeable consequences of the process, particularly bearing in mind the public sensitivity to products derived from biotechnology.

An example of such differing analysis is the attitude taken to the syndrome associated with ingestion of tryptophan made by a biotechnological route. Is the cause of the syndrome the fact that the tryptophan is the product of biotechnology, or because it contains some trace toxic materials due to the new production or purification process? *(See Biotechnology, 1992, 10, 629).*

6. I have just argued for the reverse.

7. Thus, I believe the reverse should be the case.

8. The picture in Europe is very varied, ranging from relatively relaxed procedures, to a situation approaching almost complete banning in Holland and Germany. It is very important, in my view, that the UK, in seeking EC harmonisation, avoids the temptation to give in to the latter approach, in an attempt to win harmony.

— I know too little about the Far East to comment.

— The US Government is seeking an industrially-favourable solution in which the product is the major or sole determinant. It remains to be seen whether such procedures will be politically acceptable.

9. I am not competent to comment in detail, except to say that the regulatory regime has to steer between under-regulation (likely to be the view of industry) and over-regulation (the view of the pressure groups) in such a way that consumer confidence is maintained. Thus there is a trade-off between the economic return to the industry versus the risk of not being able to establish the industry at all. Food irradiation is a well known example of a process that I and many others believe to be safe, but since it is publicly unacceptable, investment in the industry is unlikely to produce an economic return.

10. Yes, see example above, but the answer is not to abandon regulation but first to ensure that the present regime remains publicly acceptable—and that needs an active policy—and then progressively and carefully to relax the regime.

11. As always, the key issue is to maintain the confidence of the well informed, but cautious consumer. The degree of public resistance varies from one product group to another, being lowest in health and highest in food, and there is a good deal of published work available which analyses such attitudes. *(See example R. Kemp in The Release of Genetically Modified Micro-organisms—Regem 2, Ed D.E.S. Stewart-Tull M. Sussman, FEMS Symposium No 63, Plenum Press 1992, pp 99–114).*

I believe the key issue in dealing with these complex issues is openess of process, a policy which we have been seeking to implement in the ACNFP. Such a policy is alien to the political culture of this country, and is now, I believe, a major disadvantage for the future.

12. (a) Maintaining the science education process, both at undergraduate and postgraduate levels—at world standards;

(b) maintaining the cutting edge of biotechnology research at world levels, even if it means withdrawing from certain areas because of resource limitations;

(c) continuing to improve the processes of technology transfer;

(d) improving the financial resource base for risk start-up companies;

(e) above all, establishing and maintaining a consultative and open process to:

— identify new opportunities;
— determine priority assignments on an on-going process;
— rigorously review new initiatives;
— maintain, and increase political commitment at high levels in Government.

Evidence from Cantab Pharmaceuticals

The issues under consideration by the members of Sub-Committee II are of paramount importance to the future growth and success of a number of small and medium sized young companies that have their foundation in the products of outstanding British research. Cantab Pharmaceuticals (Cantab), one of the newest of these UK biotechnology companies operating in the healthcare sector, is pleased to be given the opportunity to present evidence on the regulation of UK biotechnology and its effect on global competitiveness.

1. *What is your interest in biotechnology?*

The United Kingdom has a worldwide reputation for excellence in its science base supported by internationally recognised academic centres. This reputation is further enhanced by the research productivity and commercial strength of the UK-based pharmaceutical industry.

Cantab is a biotechnology company engaged in the research and development of new biopharmaceuticals that utilise the human immune system to combat unmet clinical needs. An essential component of Cantab's strategy since its formation has been extensive collaboration with UK academic centres of excellence. The Company has close relationships with selected academic groups working in the field of therapeutic immunology to help identify and patent potential new approaches to the treatment of human disease. Cantab collaborates with these groups on the commercial development of these inventions using its own pharmaceutical research and development expertise.

The Company was founded by the former Head of Immunology of Cambridge University and a venture capital company in 1989 and now has 50 employees based in its R & D laboratories and headquarters on the Cambridge Science Park. The Company's directors and management have broad experience that spans academic and industrial research, pharmaceutical development, innovative financial management and commercialisation of biopharmaceuticals. In four years Cantab has developed special relationships with the Universities of Cambridge and Oxford to support its new product pipeline, has conducted clinical trials on its first product and became the first UK company in the biotechnology sector to succeed in a public flotation on the US NASDAQ national market system.

These achievements provide a strong base on which to develop and commercialise its products which offer new potential treatments in organ transplantation, inflammatory bowel disease, cervical cancer and genital herpes. Since each of these biopharmaceuticals presents new regulatory issues the Company has maintained a policy of close liaison with UK pharmaceutical regulatory bodies and experts from the earliest stages of development of each product. The matters under consideration by the members of the Sub-Committe are consequently highly significant to Cantab's current policies and future business. Since Cantab's business is entirely focused on ethical human pharmaceuticals the responses below have been restricted to this context.

2. *How and why is biotechnology important to UK industry?*

Biotechnology is a new and emerging UK industrial sector which arguably has greater potential for growth than any other sector at the current time. In the development of products for the prevention and treatment of disease, biotechnology is being utilised by both specialist biotechnology companies and by the major pharmaceutical companies.

Government, charity and private sector funding of basic scientific and medical research in Britain's academic institutions has provided and continues to deliver a national resource for discovery and innovation which remains internationally acclaimed. The major pharmaceutical companies have long recognised the importance of access to this source of valuable technology to maintaining leadership in product discovery and design. But the relationship between multinational corporation and academic inventor may not be the most rapid and mutually rewarding way to commercialise the benefits of this basic research.

Cantab, and other companies in the biotechnology sector, have recognised that alignment of a small and focused research-orientated business with the academic can lead to improved commercial protection for enhanced competitive advantage and more rapid product development. In the healthcare arena the existence of UK entrepreneurial biotechnology companies promises to speed the availability of new medicines and offer improved significant cost benefits to healthcare providers through improvement in disease prevention and management. As a result the pharmaceutical majors look increasingly to biotechnology companies as a source of new products.

The evidence for the potential medical and commercial success of the small company/academic interface formula is to be found in the United States. The commercial biotechnology sector in the US is some 10 years ahead of the UK. Already biotechnology drugs have been developed and have obtained regulatory approval such that novel therapies for previously untreated clinical conditions are available in the UK and other major developed countries.

The biopharmaceutical products marketed in the UK today have been developed and produced by overseas suppliers. Now, there is a real opportunity to support the growth of a significant UK industry sector with major export earnings potential. There are three key factors identifiable in the strategic vision of US administrations over the last 10-15 years which have contributed to the explosive growth of the biotechnology industry in the US.

- close liaison between industry management and existing Federal and State regulatory bodies to create a regulatory environment that speeds delivery of the benefits promised by new drugs
- provision of a fiscal policy targeted to the needs of the sector to support rapid growth of entrepreneurial businesses
- declaration of a Federal policy to be the worldwide competitive leader in the business of biotechnology

The UK is now positioned to compete as a major innovative force in the biotechnology sector. A small number of British companies, including Cantab, British Biotechnology, Celltech and Xenova, have succeeded in gaining an international reputation for their science and business achievements. It is important that the correct regulatory and fiscal environment is now set such that these companies, and other companies which support the industry infrastructure, can compete effectively with US companies and generate a new and profitable UK business sector.

3. *What future prospects and opportunities does the technology offer?*

Biotechnology products and processes address fundamental human healthcare needs of people in developed and developing countries. Pharmaceuticals and vaccines have enabled breakthroughs in the prevention, diagnosis, treatment and management of human disease. In the last 5 years several biopharmaceuticals have reached the market—these include hepatitis B vaccine, human insulin for the treatment of diabetes, erythropoetin for the management of end-stage renal disease, tissue plasminogen activator for the treatment of heart attacks and colony stimulating factors for the enhancement of cancer chemotherapy. There are many other products in the pipeline which stand to revolutionise healthcare into the next decade. Moreover, the products of pharmaceutical biotechnology promise to offer significant cost benefits to the management of healthcare in the UK and other developed countries.

Cantab is concentrating its R & D activities on two series of products for disease management:

- Leucocyte Modulators which block or regulate immune function. Current products under development include monoclonal antibody drugs to prevent acute rejection of transplanted organs, which occurs in over 50 per cent of the 20,000 kidney transplants performed annually worldwide and biological drugs to treat Crohn's disease, a debilitating chronic disease which affects over 350,000 people worldwide for whom current therapy is inadequate.
- Therapeutic Antigens which stimulate immune responses to disease-associated viruses. Current products under development are based on engineered viruses and focus on the treatment of cervical cancer, which causes 12,000 deaths each year in Europe and the US, and the management of recurrence from genital herpes infection, a chronic disease effecting more than 10 million people.

The Company believes that these new immunological approaches to the prevention and treatment of problem diseases represent a significant business opportunity which when combined with developments in other UK biopharmaceutical companies forms the basis of a highly productive and competitive new business sector.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

The emergence of the biotechnology industry, spawned by the discovery of gene technology some 20 years ago, has benefitted from innovation and leadership by outstanding international scientists who have, from the outset, faced up to the regulatory and moral issues that would face the sector. This has meant long-term co-operation and dialogue between those scientists and regulators in the UK, other European countries and the United States with a resultant collaborative approach to the modification and development of existing regulations. This means that these regulators have been able to accommodate new processes in the context of their application to different sectors of public and industrial importance.

Products manufactured using biotechnology processes usually fall within existing regulatory frameworks that have been developed for the target industry. For example, the development of pharmaceuticals utilising biotechnology is tightly regulated from experience over many years in the development of vaccines, antibiotics and blood or tissue derived products. In the case of Cantab's products, the existing regulatory environment in the UK (NIBSC, MCA, CSM), EC (CPMP) and FDA (Center of Biologics Evaluation and Research Division) support the issues raised in the development of safe biological drugs. Since the therapeutic approaches being developed by the Company are innovative, new specific regulatory issues have been and will be raised relating to design of products and their intended use. Cantab has worked with the existing biologics regulatory bodies and their expert advisors to resolve these issues on a collaborative basis. This has been found to be a pragmatic and productive approach. In summary, the techniques of biotechnology as it relates to the development of new biopharmaceuticals are unlikely to raise regulatory issues which are beyond the scope of experience of existing regulatory bodies and their expert advisory panels.

5. *Should biotechnology be regulated by an industry-specific regime?*

The regulatory framework for the products of biotechnology already exists in developed countries. It would not be possible for an industry-specific regime to gather the necessary knowledge and experience to tackle the many applications of the use of biotechnolgy processes. It is more important that the regulatory addressing each particular product and application sector and work with the biotechnology innovators in the further development and improvement of existing regulations to accommodate new innovative processes. A model of this appraoch is provided by changes in the structure of the US Food & Drug Administration to address new technologies that underpin existing applications and needs, such that the benefits of novel products fulfilling unmet needs can be brought rapidly, safely and cost-effectively to market.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by the characteristics)?*

Vertical regulation is preferred. It is important to eliminate the need for multiple approval processes by adopting a pyramid structure to accommodate different regularoty issues on a particular product. For example, the development and approval of a live virus-based therapeutic or product should be reviewed by a single regulatory agency empowered to assess the safety, efficacy and environmental impact of use of the drug in the context of the disease to be treated. If these review processes are separated, and become the responsibility of different regulatory agencies, the impact may be to delay delivery of the benefit of the therapy and would in the long term deter against innovation in these types of technology.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

At the current time, the regulations for the management of genetically manipulated organisms (GMO's) has, in the UK, focused on the agricultural sector. Cantab's development of Therapeutic Antigen products, which can involve the use of engineered live viruses, presents a need to establish different guidelines for GMOs specifically in the context of prevention and treatment of human disease. Inevitably regulations developed for agricultural purposes are not wholly appropriate and therefor Cantab has been working with a number of different UK regulatory bodies lead by the HSE (ACGM), MCA and NIBSC to establish sensible guidelines on a case by case basis. Concertation of these regulatory bodies, under the sole leadership of a single end-use regulator (eg MCA) would lead to development of regulation that supports such innovation. This is a prime example of the need for shift into a vertically integrated approach to the regulation of biotechnology products.

8. *How do current regulations compare with those of other competitor countries?*

Cantab's views on this matter have been fairly represented by the response of the UK BioIndustry Association.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards:*

1. Research

A complex regulatory regime may result in escalation of research costs which, given other financial constraints experienced by the UK academic and corporate biotechnology sector, would result in a slowing of the product innovation process compared with overseas competitors.

2. Product development

Investment in the commercial development of new biopharmaceutical products and the corporate infrastructure to develop and manufacture these drugs will continue to shift to countries which provide a more favourable regulatory environment balancing the risks with the potential product benefits.

3–4. Investment and Location

Several major European pharmaceutical companies have elected to invest in product research, development and manufacturing operations outside of Europe because of a more favourable regulatory environment elsewhere. As UK biopharmaceutical companies advance their products to the later stages of clinical development similar decisions, as to where to place large scale investment of manufacturing operations, will be faced. Certain of these companies are already investigating or pursuing US operations in preference to UK expansion. It is not yet too late to provide an incentivised financial and regulatory framework to ensure that this valued investment in industrial development is retained in the UK.

5. Sales and Marketing

US biopharmaceutical companies have one single distinct advantage over their European competitors in the sales/marketing arena—they are centred in an advanced single healthcare market which is vertically regulated through Federal groups and where competitive protection is afforded through unified patent law. Regulatory approval and commercial exploitation of that single market can provide sufficient return on investment on the operations of those companies without recource to export marketing. in contrast UK-based biopharmaceutical companies must rely on export for commercial success and this presents complex regulatory, patent and marketing challenges. It is true tht this complexity is also faced by US competitors, but many have chosen to pass these difficulties to major European pharmaceutical companies that are resourced to cope with these challenges, in exchange for a reduced return on investment.

The CPMP high-tech concertation procedure for the regulation of biotechnology drugs is a desirable framework on which to build. It is important that regulatory issues raised by new biotechnology inventions are addressed in the context of the CPMP umbrella.

11. *How best can issues of public acceptance be addressed?*

Cantab's views on this matter have been fairly represented by the responses of the BioIndustry Association.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

Investment in Basic Research

Government support for basic research through the Research Councils continues to decline in real terms and has resulted in gradual attrition of the UK's capabilities relative to the United States and other European countries. Britain's biotechnology companies and the UK pharmaceutical industry have responded by increasing the level of investment to support technology development and in certain circumstances contribute to basic research. Inventions arising from basic resarch funded by the Universities, SERC, MRC and AFRC have provided a platform for technology and product development in the biotechnology industry. Private sector funding inevitably is more directed and polarised in its commercial outlook and therefore is unlikely to foster the same type of creative innovation as public sector funding. It is essential that the government continues to support and accelerate investment in academic research to assist UK biotechnology companies in keeping pace with their US competitors.

Patents

The pharmaceutical and biotechnology industry places great emphasis on obtaining competitive advantage through intellectual property rights. US patent law favours the US inventor through the "first to invent" priority system. UK patent law, consistent with other European countries based on the "first to file" priority system. Progress has been slow on harmonisation of patent legislation to provide equal competitive opportunity, but must continue to be supported in the UK and the EC.

Finance

The availability of finance to fund UK biotechnology is a key factor for success of the already established UK biotechnology companies and as a catalyst for expansion of the business sector.

Drug discovery and the subsequent development of a product through to marketing is a process that can take eight to ten years. For a start-up biotechnology company with, as yet, no revenue stream through product sales this represents a substantial length of time to finance the development of products. The investment required for each biopharmaceutical product may range from £50 million to £100 million.

Venture capital finance from specialist biotechnology investment funds has proved to be a reasonable source of finance for start-up biotechnology companies in the UK. This type of finance has been attracted from UK, US, European and Japanese venture capital fund managers looking to invest, on a long term basis, early stage finance at a relatively low cost on a high risk/potential high return basis. The timing of this type of investment is such that the start-up will, at the time of investment, have added minimal value to the company and therefore a substantial amount of equity can be bought in the company at a low price. This enables this type of investor to take a position in a number of companies and by doing spread the risk.

UK venture capital has proved a limited source of finance and so there is a need for a review of other potential mechanisms to provide financial incentives to UK biotechnology companies to assist in their early stage development. The US administration has provided several Federal and State initiatives to assist biotechnology companies in both the development of pharmaceutical products and the substantial investment required to put in place corporate infrastructure to develop and manufacture these products.

After the start-up years a new challenge faces biotechnology companies: mezzanine financing. As additional value is added, and finance is raised through further rounds of venture capital at an increasing price per share, a point is reached when the relative cost of equity becoms less appealing to venture capitalists and further investors for a company at this stage of development are difficult to attract. This is particularly the case if there is no apparent exit route for the investors.

US biotechnology companies have demonstrated that this financing gap can be addressed through either the private placement of shares to high net worth individuals and targeted institutions or through public flotation. The US Securities and Exchange Commission and The Nasdaq Stock Market have for many years provided a route for institutional and retail investors to access equity in early stage companies. The US biotechnology sector has used this route as a financing vehicle to support pharmaceutical discovery, development, manufacturing and marketing to the point of product launch. In 1992 both Cantab and British Biotechnology decided to access this source of development stage finance and succeeded in completing initial public offerings on the NASDAQ exchange.

At a time of public flotations biotechnology companies have been able to attract the type of investor that does not wish to take as much risk as the venture capitalist but still believes that there is substantial opportunity for capital growth, especially as it would be highly unlikely that any form of dividend would be payable in the foreseeable future, and is prepared to pay a premium for the liquidity of the investment. As a result of a company going public the venture capital fund managers gain the necessary liquidity in their initial investments to release funds for new investment in other new biotechnology start–up companies. This cycle has no doubt led to providing the finance foundations upon which the US has been able to build up a very strong biotechnology sector, which now leads the world.

It is vital that, on a similar basis, UK biotechnology can identify sufficient finance to enable it to realise its full potential. The excellence of UK academia has already been discussed and its ability is evidenced by the fact that the UK is the leading European country in biotechnology and that the emerging sector of UK biotechnology companies has been able to attract substantial overseas investment, predominantly from the US despite intense competition from the US biotechnology sector list.

Success of the UK biotechnology industry is likely to lead to considerable funds flowing into UK academia through royalty streams on product sales, beneficial export trade and the growth of a sizeable infrastructure supporting the sector. For this success to be realised, access to public finance is needed through the relaxation of the present listing requirements of the London Stock Exchange (LSE). This would then enable the wealth that the sector generates for UK investors to be re-invested into the UK, either within the sector or otherwise.

To support such an initiative by the LSE it would be particularly beneficial if a UK retail sector could be established to invest in high technology companies, as has been the case in the US through tax incentives which in part would compensate for the lack of dividends, and particularly so if the UK maintains low interest rates attracting investment into equities and away from cash deposits. Equally tax incentives could be introduced to attract a greater number of entrepreneurs to leave the safety of academia and to start up new companies. In particular, a reduction in the rate of capital gains to a capped level would provide a strong financial incentive.

Evidence from Celltech Ltd

Synopsis

Celltech is a biotechnology company which develops and manufactures pharmaceuticals. In general we are satisfied with the current mechanisms for regulating our sector of the industry with the Medicines Control Agency regulating safe use of the products and the Health and Safety Executive regulating safety in the workplace and the environment. We are however concerned at the increased levels of administration required to satisfy the new GMO regulations particularly for activities which are assessed as being very low risk.

Question 1. What is your interest in biotechnology?

Celltech is using biotechnology to develop two businesses. The first, Celltech Research, is using recombinant DNA and monoclonal antibody technology to develop novel therapies for life threatening diseases such as cancer. The second business, Celltech Biologics, provides a contract manufacturing service to the pharmaceutical and biotechnology industries based on its skills in the large scale production of therapeutic proteins, especially antibodies, from animal cells. The company is the world leader in this area and exports a large proportion of its output, particularly to the USA.

Question 2. How and why is biotechnology important to UK industry?

Within our own sphere of interest biotechnology has become an essential component of drug discovery in the pharmaceutical industry. It is also important to an increasing number of companies providing services to the pharmaceutical industry; for example reagent suppliers and testing laboratories.

Question 3. What future prospects and opportunities does the technology offer?

Within the pharmaceutical industry, biotechnology is playing an increasingly important role in drug discovery. The technology is being used not only to produce "first generation" protein drugs such as antibodies and hormones but also, and more importantly in the long term, to provide a more effective route to the discovery of chemical drugs. Biotechnology also provides the basis for achieving cures for some genetic diseases by gene therapy and the eradication of others by novel vaccination strategies.

Question 4. Which developments in biotechnology raise issues of safety and how should they be addressed?

The developments in biotechnology that raise issues of safety can be divided into

(A) recombinant host cells
(B) recombinant proteins
(C) recombinant vectors

A. Recombinant Host Cells

Host cells used for the expression of recombinant products can be divided into two categories:

(i) microbial
(ii) animal

Microbial cells, including bacteria, yeast and filamentous fungi can exist as free-living organisms whilst animal cells cannot grow or live outside the body, unless provided with a carefully-controlled environment. Accidental release of animal cells represents a low hazard. Microbial cells are more robust than animal cells and may be able to live outside of the laboratory or production facility. To reduce the risk that recombinant microbial cells will grow outside the laboratory environment, disabled strains are used, which cannot compete with wild type strains neither can they efficiently transfer their DNA to such wild-type strains. These measures minimise the risk that recombinant host cells can escape into the environment, establish themselves and transfer deleterious genes to organisms that may subsequently colonise man, other animals or plants.

Because of the precise nature of recombinant DNA technology in most instances, the recombinant DNA transferred to host cells is fully characterised, thus ensuring that unwanted or deleterious products are not produced.

Animal cells used as recombinant host cells, are relatively safe in terms of escape into the environment, since they cannot exist outside of the laboratory or production facility. The animal cells commonly used in the pharmaceutical industry may sometines contain viruses but these are characterised and shown to be non infectious for human cells. In those research applications where viruses which infect humans are used, higher containment is employed.

Assessment of risk is not limited to the properties of the host organism. The properties of the recombinant gene product (protein) is assessed as described in B below.

B. Recombinant Proteins

Recombinant proteins produced in the pharmaceutical industry by this technology are, in many cases, biologically active and highly potent. These may pose a risk if they could be introduced into the environment or directly into man, by a suitable route and in sufficient quantity to exert a biological effect. Proteins are large molecular-weight entities that fail in most cases to gain access to animals unless directly injected. If such proteins are swallowed, for example, they are broken down by the digestive system. Proteins do not in general penetrate the skin or internal body surfaces. Hence the risk posed by recombinant proteins is very low.

Considerable interest has been displayed in the role of particular proteins in cancer initiation and cellular proliferation. The genes encoding these proteins are called oncogenes. Although no special properties are attributed to these proteins that might allow them to gain access to the body, recombinant organisms expressing these proteins are treated under higher containment than those expressing non-oncogenic proteins.

C. Recombinant DNA Vectors

Recombinant DNA Vectors are the means by which DNA is manipulated and transferred. In general these vectors only efficiently enter cells after the use of physical techniques designed to make cells take up the DNA. Hence, the recombinant DNA per se, represents little risk. A potential risk of tranfer of recombinant DNA into cells results from the use of infective, viral vectors, particularly those capable of infecting human cells. This type of work underpins the development of gene therapy. The use of infectious, recombinant viruses is carried out under higher containment levels.

Regulation of Recombinant Work

The regulation of recombinant DNA work is addressed by the legislation currently in force, where a risk assessment is required, based on scientific principles. Other safety issues concerning the large scale use of micro-organisms are addressed by the Health and Safety at Work Act and regulations such as COSHH. The current system of regulation of genetic modification work is appropriate, with the collaborative approach of HSE inspectors and guidance from ACRE, ACDP and ACGM who are expert in the field.

Therapeutic protein products derived from recombinant organisms are regulated through the national agency responsible for approving drugs for marketing. (MCA in UK and FDA in USA). International agencies are working towards harmonisation of testing requirements, a move which will benefit companies in this sector. Within Europe the multi-stage concertation procedure for review of biotechnology pharmaceutical products has also been a significant step forward.

Question 5. Should biotechnology be regulated by an industry specific regime?

Biotechnology is currently regulated to ensure that the product itself is safe and effective, the workers in the biotechnology industry are not exposed to harmful substances, and that the environment is protected. The current system in the UK pharmaceutical industry is that the Medicines Control Agency is responsible for the quality of the product and its safe use, whereas the HSE is responsible for worker and environmental safety through a system of inspections. The HSE inspectors are not industry specific, but have expertise in biotechnology. Thus in general terms, the product is regulated on a sector-specific basis, whereas worker and environmental safety is regulated on a process basis. This seems wholly appropriate in the context of biotechnology in the pharmaceutical industry.

Collaboration between the agencies should continue. There are very few examples where the requirements of the agencies conflict, and these have been resolved with engineering or procedural methods, usually in consultation with the agencies.

Question 6. From a technical point of view, is horizontal regulation better than vertical regulation?

(see above)

Question 7. Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?

For the pharmaceutical industry this evolution would not be an efficient or economical use of existing specialist expertise within the regulatory bodies, unless a major realignment of agencies takes place. We find no difficulty in working with more than one agency.

Question 8. How do current regulations compare with those of other competitor countries?

Question 9. What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards:

(1) Research.

(2) Product development.

(3) Investment.

(4) Location.

(5) Sales and Marketing?

There are three concerns about the regulations which apply to all these areas of activity:

(a) The administration time and cost spent in preparing documents, which require many details of the micro-organisms, is considerable, even when risk assessment leads to the conclusion that the organism is low risk.

(b) The delay in waiting 60 days before some micro-organisms can be imported or stored will be a significant disadvantage for UK and European contract manufacturers.

(c) The disclosure of commercial information is a major concern. The perception that information could be disseminated among Member States will be a competitive disadvantage to Celltech's contract manufacturing business. The administrative load of dealing with confidentiality issues will again be excessive for those micro-organisms which are assessed as being low risk.

Question 10. Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?

The new regulations will impact on the amount of research carried out in UK academia. The additional administration required by the regulations will be a cost penalty on the already stretched resources of UK academia.

The regulations are also likely to lead to delays in the initiation of experimental research. This is an important issue, since the patenting of discoveries is central to the biotechnology industry and the USA has significant advantages in terms of claiming priority dates. Current changes to the regulations do not appear to reduce the risk associated with recombinant DNA work, only to increase the amount of information and notification required. The previous categories of containment are retained in the new regulations.

Question 11. How best can issues of public acceptance be addressed?

In the area of pharmaceutical research, our perception is that the public is not concerned with the technology underlying the discovery of new medicines. Rather they are more concerned with the importance of the therapeutic effect (ie, treatment of something worthwhile such as cancer) and the absence of adverse side effects (avoiding another thalidomide). Both of these concerns are dealt with by effective regulation of pharmaceutical products. We believe that if National (MCA) and European organisations (CPMP) emphasise their active role in regulating new medicines, then this can only be helpful to the industry.

Unfortunately, organisations such as the MCA are not very newsworthy. Furthermore, professional organisations such as the ABPI are hindered by their vested interest in the pharmaceutical industry. This leaves the major medical charities (ICRF; CRC; British Diabetes Association; Wellcome Trust; Arthritis and Rheumatism Council) as the groups most likely to affect public policy by virtue of emphasising our need to improve medical treatment of many human diseases and the need to exploit new technologies to achieve these advances.

Question 12. What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?

For most start-up biotechnology companies in the pharmaceutical area their major problem is funding, given that product development can take 7–12 years. During all this time the Company will probably be loss-making. The availability of funds is the natural attraction of the USA both in terms of access to venture capital and to major capital markets. The stock exchange has just published guidelines for flotation of emerging pharmaceutical companies which are quite onerous in comparison to those which exist in the USA. For example, in the UK a company must have two products in clinical development whereas in the USA the requirement does not exist. This will prove to be a major barrier to small single product companies.

A key factor will be the overall level of investment in Biology research in Universities and Research Institutes, since this is the foundation of our industry. This investment should have the objectives of fostering creative discovery research and not copying current applied industrial research, of encouraging scientific entrepreneurs to leave Universities and found their own businesses and to provide a rewarding career structure that encourages young scientists to take up research.

Evidence from the Chemical Industries Association (R J Grainger OBE, Director Product and Regulatory Affairs)

Thank you for inviting the Chemical Industries Association to give evidence to the above sub-committee. Our answers to the questions posed in your letter are given below.

Q.1 *What is your interest in biotechnology?*

The chemical and allied industries have a broad interest in biotechnology. This interest is related to:

- the use of novel feedstocks
- the use of more efficient and environmentally friendly production techniques, eg, enzymes to produce chiral molecules of only one form
- the use of detection methods eg, to detect discrete chemiclas in waste streams
- environmental clean-up eg, the use of genetically modified organisms to remove certain substances which present a problem in waste streams.

We believe that biotechnology will have a significant effect on the chemical industry in years to come. At the present time 30 per cent of our members use biotechnology against 10 per cent five years ago. This trend is, we believe, likely to increase, particularly with "off the shelf" diagnostic and waste treatment kits.

Q.2 *How and why is biotechnology important to UK industry?*

The key to economic growth in the UK is the production of high added value products using new technology. In order to take advantage of biotechnology it is essential that we have in place an economically encouraging legislative framework.

The chemical industry today faces pressures never before seen. Our access to markets is becoming more difficult and competition from around the globe, notably South East Asia, is growing. Additionally, we are faced with ever more stringent legislation, principally of an environmental nature.

We believe that through using the tools available to us with biotechnology we can hope to compete with our international rivals in regard to fine chemicals. Environmentally, the techniques of biotechnology, in many cases, offer a far superior route to the same product via a more environmentally benign process, which is also often cheaper.

Q.3 *What future prospects and opportunities does the technology offer?*

Modern technology offers many potential advantages to society in general and to developing countries in particular. These benefits can be in the form of improved yields, greater nutritional value in food products, better resistence to disease or drought, salinity, acidity or alkalinity, or pest attack, whether applied to food or cash crops. Moreover, new or improved pharmaceutical and veterinary products derived from the application of modern biotechnological techniques can offer significant advances in human and animal health including better disease vector control. Major opportunities also exist in the development of emission control and environmental clean up technology using modified micro-organisms.

For the chemical industry in particular, existing chemicals can be produced via new routes, more cheaply, efficiently and to a higher degree of purity.

Q.4 *Which developments in biotechnology raise issues of safety and how should they be addressed?*

There are safety issues which we feel we have successfully addressed and have subsequently had no difficulty with. This has been due to open discussion with academics, industrialist and employee organisations.

We believe that general concerns that novel genes resulting from genetic modification could spread amongst the natural gene pool are unfounded. Intensive research by government and industry has failed to demonstrate that this occurs. Considerable sums of money are being spent in conducting risk assessments. Research knowledge currently available allows evaluation of potential risk and evaluation of experimental safety before actual release experiments are conducted.

Q.5 *Should biotechnology be regulated by an industry specific regime?*

The CIA believes it is essential that the strategic importance of biotechnology to the economy of the European Community and the UK, in particular, is recognised and appropriate regulation is put in place to cover manufacture and use.

It would appear to us to be entirely proper that Regulation should be required only on the requirements of safety, efficacy and quality of a final product.

Q.6 *From a technical point of view is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics).*

CIA can see no justification for a product to be judged by its method of production. For marketing purposes a product should meet the criteria of safety, efficacy and quality. In terms of a chemical produced through a biotechnological process, the end product is chemically the same as one produced through traditional techniques. As the chemical industry is already heavily regulated through existing product legislation we can see no grounds for additional legislation.

Q.7 *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

The chemical industry is already heavily regulated and we believe satisfactory mechanisms are already in place to protect man and the environment within current chemical legislation. Recent regulations on contained use have added to the regulatory burden in the UK for the chemical industry. We would therefore support all chemicals being legislated for through "vertical" instruments.

Q.8 *How do current regulations compare with those of other competitor countries*

- in Europe
- in the Far East
- in the USA

As far as we are aware only Denmark, Germany, the Netherlands and the UK have adopted the Directives on Contained Use and Deliberate Release. Different interpretations have been made in each of these countries. For example, in Germany, the Gene Law has been used as the vehicle for control. This has traditionally been so restrictive that it is currently being reviewed by the German authorities, who are additionally seeking amendments to the EC Directives of concern. It may be of interest that the UK lost two major contracts to France in this area within the last 12 months, a decision based partly on our regulatory regime.

Japan operates a system based on guidelines rather than Regulation where operations and products are not discriminated. A wide range of government departments have drawn up guidelines including the Ministry for Education, Industry, Health and Welfare and Agriculture, Forestry, Fishing and Food.

The USA have complete Regulations covering the products of biotechnology where operations and products are again not discriminated. Their general approach to biotechnology is one of encouraging its use and indeed this approach has come from the White House through the Bush and Clinton administrations.

Three agencies have the principal regulatory authority in the USA. These are the Food and Drug Administration (FDA), the US Department of Agriculture (USDA) and the Environment Protection Agency (EPA).

The FDA is the statutory authority covering a very broad range of product and processes. The FDA enforces the Federal Food, Drug and Cosmetic Act and parts of the Public Health Service Act. The jurisdiction of the FDA extends to human and animal drugs, foods, food additives, human biological products, cosmetics and medical devices. The FDA review rDNA products on a case by case basis with emphasis on the product rather than the process. The FDA uses documents entitled "points to consider"; these contain guidelines for interpreting and analysing the way FDA regulations apply to biotechnology products. This procedure has proven to be flexible when dealing with product developments, from a fast changing technology base. The FDA has had a significant influence on the commercialisation of technology.

Further, the US National Institute of Health (NIH), has been involved with rDNA techniques for a number of years and has been instrumental in formulating the regulatory framework. The guidelines put in place by the NIH have been widely followed by industry.

Regulations in the US would appear to be as wide ranging as ours though the level of bureaucracy appears to be far less and therefore notifications are much quicker.

Q.9 *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards*

(1) research

(2) product development

(3) investment

(4) location

(5) sales and marketing?

Research We believe that the new Regulations on contained use and deliberate release will have a significant impact on both industry and academia. The Regulations will be expensive to operate and are likely to push industrial research to other countries. However, for our universities this is not possible. Increased costs means less research and in the long run less innovation, with a gradual erosion of the science base in this country. Indeed in 1991 the House of Lords Select Committee on Science and Technology published a first report on "Innovation in manufacturing industry" which defined the primary purpose of the science base as: "to provide well-educated, skilled and adaptable staff, to encourage the study of scientific and technological subjects and to carry out basic scientific research". We fear that regulation in the area of biotechnology will have a detrimental effect on the development of the science base in this area.

Product development At the present time the chemical industry feels that existing legislation affecting genetic modification is both complex and bureaucratic.

Investment Within the UK there is a well established venture capital system, however, much of the money available for biotechnology projects appear to be going to the US. There are a number of reasons for this, only one of which is the difference in regulatory approach.

Location CIA has, over the last 12 months, been presented with two examples where we have lost major contracts to overseas competitors. This loss, we are told, was for a number of reasons, one of which was the regulatory regime prevalent in the UK.

Sales and marketing We are uncertain at the present time what constraints will be placed upon industry in selling and marketing the products of biotechnology.

Q.10 *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

As discussed earlier we feel that the science base upon which biotechnology is built will be diminished over the coming years due to the stringency of the new Regulations. There is growing evidence that developments which have been made in the UK are being manufactured and marketed by foreign companies. Within the chemical industry this has however been less evident and we forecast is likely to remain so.

Q.11 *How best can issues of public acceptance be addressed?*

We feel it is important to first understand why the public acceptance of biotechnology is falling. The word "biotechnology" projects a negative image, combining "life" with "technology" in an era when technological progress is not universally seen as benign nor its practitioners trusted. The general level of technological understanding in the community is low. This is said particularly to be the case in Britain. Whether this is so or not is debatable, but it is certainly true that science is becoming ever more specialised and the gap between experts and the public is inevitably widening.

Survey have shown that only 28 per cent of Britons and 25 per cent of Americans know that antibiotics are ineffective against viruses. The publicity given to the discoveries of Watson and Crick and the comparative familiarity of the word "DNA" has no doubt led to the following result in a recent poll:

"When scientists use the term DNA, do you think it is to do with the study of:

	(%)
Stars	1.8
Rocks	1.8
Living things	43.2
Computers	6.9
Don't know	46.1"

(Durant, Evans and Thomas. **Nature** 340pps 11,14,1989)

But even so, less than half of the population make this connection. However, surveys have made the point that self-reported levels of interest in science topics are high despite low self-reported levels of knowledge, this contrasts sharply with what one might call "arts" subjects where knowledge may be high but interest low. If this is so, television programmers need to be more finely tuned to the needs of their audience.

The difference between public understanding and public ignorance of science may, it has been claimed, be the difference between respect and admiration on one side, and hate and fear on the other (Azimov, 1. **Nature** 306, p11 1983).

In conclusion we would draw attention to the following:

1. Those biotechnological activities widely accepted as benign should be used in helping the public to recognise this technology as one which is helpful.
2. Ethical concerns must be treated with sympathy and consideration on a case-by-case basis, recognising that the argument is generally unwinnable on a basis of rationality.
3. Explanations about safety will inevitably require an unusual level of technical education. This will demand substantial resource and persistence.
4. Countering entrenched stereotypes about scientists and "big business" will require the same elements of dialogue, sympathy and sensitivity that have been recommended for the chemical industry as a whole.

Q.12 *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

We see three factors affecting the development of the use of technology:

1. The first of these is the legal protection of intellectual property. It is essential that effective patent legislation in biotechnology is avialable if Britain is to develop as a centre of excellence in this field. The stakes are high. The CIA believe that Europe must develop a legal framework which encourages this growth.

   At the present time, an EC proposed Directive on the legal protection of biotechnological inventions is being discussed in Europe. The directive is, essentially, concerned with ensuring that the patent offices and the courts throughout the Community apply the established law in the European Patent Convention in a uniform manner. There are fears that, especially in countries where there is no specialist patent Court, the law will be applied in widely different ways, which are adverse to the establishment of a Single Market.
2. Secondly, we have concerns that it is not easy for biotechnology using companies to raise money for projects including the use of biotechnology. However, recent proposed changes announced from the London Stock Exchange give us cause for hope. The proposed new rules will allow companies "without an adequate trading record" to become listed under certain circumstances. The circumstances which they mention would appear to include pharmaceutical companies only, but nevertheless the principal has been set and we look forward to a broader range of young companies being welcomed to the stock market. It is worth pointing out that even for listed companies it can be difficult to raise finance for such projects due to poor public perception.
3. The final hurdle which we see to many companies using this technology is one of ignorance. Biotechnology may seem to many business managers as an area where high start up and research costs are incurred. For the chemical industry, where diagnostics and the use of enzymes in cleaning up effluent this is not the case.

CIA will of course be happy to provide details on any item discussed above.

Thank you once again for the opportunity to comment.

Evidence from Ciba Pharmaceuticals (Dr Alan White, Director of Research & Preclinical Development)

CIBA-GEIGY AG (referred to nowadays as Ciba) is a global chemical company with headquarters in Basle, Switzerland. In 1992 it had world-wide sales of 22.2 billion Swiss francs and employed 90,554 people. Of these sales 8,662 billion SF were in Healthcare and 4,817 billion SF were in Agricultural products. The remaining sales were in industrial chemicals. The future growth of the company depends to a significant extent on the introduction of new products from its biological divisions into world markets, some of which will undoubtedly be "biotechnological" in nature. Ability to research, develop and market these new chemical entities in various regions of the world will depend on the balance between a number of factors. However, in all sectors of activity the regulatory environment will play a significant part in discussions where inward investment into another country is being actively considered.

RESEARCH

At present Ciba carries out research in biotechnology mainly in Switzerland (Basle) and in the USA. In the Pharmaceutical Division these research efforts are directed towards new products mainly in the areas of blood coagulation, cancer, viral infections and wound healing. Genetically produced vaccines against major viral and parasitic infections are also under development. Some of the work is undertaken through alliances with companies in the USA.

In the Agricultural Division major thrusts are being made in plant biology towards the production of plants with specific in-built characteristics designed to improve survival, through pest-resistance, and marketability through improved customer acceptability.

The siting of research centres in Switzerland and the US rather than the UK was not due to regulatory restrictions in the UK relating to safety. From the research point of view the UK would still be an equal contender. However, there are other considerations. The biotechnology culture in the USA is strong not only in universities and research centres but industrially where a large number of start-up companies have grown over the last 10 to 15 years. Some (eg Amgen) have reached full maturity. The UK has not kept pace with this development. This shortage of venture capital combined with inhibiting stock exchange regulations have restricted the rate of start-up of small companies so the number of such biotechnology companies is still relatively small. In addition, because of the tendency by the government to underfund the science base, including HEI's, as a per cent of GDP, the number of qualified scientists and skilled workers is not as high, per capita, as it should be. The restrictive factor in setting up biotechnology research in the UK is therefore more likely to be due to uncertainty over the acquisition of scientific talent than to other factors.

Research projects in biotechnology are usually carried out on a small scale using highly qualified and trained staff. In the UK Risk Assessments as required by the Health and Safety at Work Act (HSAWA) and Control of Substances Hazardous to Health (COSHH) are always made. These requirements are probably no more onerous than in the rest of Europe or in the USA.

Development

During development of a product derived from biotechnology scale-up has to take place in order to supply material for clinical trials, in the case of a pharmaceutical product, and for field trials for a potential agricultural product. At this point public perceptions and misperceptions are likely to be aroused and faith in national legislation, guidelines and codes of practice is of utmost importance if projects are to succeed in a timely fashion. Here it has to be admitted that the situation in the UK appears not to be very satisfactory. In the USA and France and Belgium regulations allowing field testing of agricultural products are enacted. Much data has been accumulated world-wide and through the use of these data the tendency in the USA is to relax regulations in the light of experience. For some crops there would only now be a simple notification procedure. Thus Ciba and indeed any other large company can make proposals to carry out field trials on a relatively large scale now in the USA in a reasonable time and with minimum bureacracy.

In Europe separate negotiations have to be carried out with each country. More importantly these negotiations have to be conducted in the light of each country's interpretation of European Directives 90/219 (contained use of Genetically Manipulated Organisms, GMOS) and 90/220 (deliberate release to the environment and marketing of GMOS). All member states are finding these directives difficult to interpret. In the UK the guidelines developed from the directives have had to proceed through a large number of re-writes to produce documents which are usable and which offer practical solutions. However, when clarity is difficult to achieve loopholes are likely to appear and the confidence of the public becomes eroded. Ciba has not tested the regulatory environment in the UK. In 1992 field trials of maize, genetically engineered by Ciba to resist the European Corn Borer, were carried out in France.

In addition to the above-mentioned Directives 90/219 and 90/220 the European Commission, at the present time are still unwilling to drop the proposal for a Directive on the transport of GMOS. All member states are opposed to this, feeling that existing legislation is sufficient.

Commercialisation and Marketing

In the case of pharmaceuticals, products of biotechnology would be subject to the laws and regulations which exist in the UK to safeguard patients, pharmaceutical workers and the public. Within a few years Ciba will be marketing hirudin in the UK and no special problems are expected. Clinical trials have already been conducted here without problems. Hirudin is a highly specific anti-coagulant from the leech. The appropriate genes have been transferred to yeast and therefore it can be manufactured on a large scale using fairly conventional fermentation technology.

Commercialisation of agricultural products is not so far advanced. So far as is known two applications for commercial registration of r-DNA crops have been made by companies other than Ciba: Florigene for white chrysanthemums in Europe and Calgene for the FLAVR-SAVR tomato in the US. The latter, being a food, has resulted in some controversy. However, the US regulators have produced a set of procedures for Calgene to follow so that tomatoes can be grown in farmers' fields. In the EC, including the UK, there are, as yet, no community-wide procedures and the EC is still struggling with Council regulations to cover r-DNA products as foods or components of food. Here, the UK is likely to be held back with the rest of Europe.

Intellectual Property

The Commission of the EC is at present making proposals for a directive on the legal protection of biotechnological inventions. A Council common position cannot be expected before September/October of this year. There are two points in the proposals to which the European Federation of Pharmaceutical Industries (EFPIA) is violently opposed. These are the introduction of the so-called "farmers privilege", which could set a precedent for similar privileges for other interested groups, and the introduction of compulsory licences between two different groups and independent types of intellectual property rights, eg patents and plant variety rights. There are other proposals which, if watered down, could lead to an unsatisfactory state of affairs.

PUBLIC PERCEPTION

The public, being for the most part in a state of ignorance concerning science, are bound to be frightened of biotechnology. They will be concerned with the possibility of accidental release of micro-organisms and their misuse and, in the case of food with product safety. Ethics and emotions also come into the equation. These public concerns can only be met through education and accurate reporting in the media and through regulatory procedures and reference committees in which the public has complete faith. Ciba has had a bad experience in this regard. Due to the activities of "fundamentalists" as described by Dr Alex Krauer, CEO of Ciba in his Annual Address to Shareholders in 1991, planning permission for the building of a Biotechnikum in Basle for the production of genetically engineered products including hirudin could not be obtained. Instead, in 1992 Ciba decided to make the investment at Huningue in France.

VERTICAL VERSUS HORIZONTAL REGULATION

As the name clearly states "Biotechnology" is not an industry it is a technology with applications in a variety of industries from waste management to foods. It is therefore the view of Ciba that control should be exercised vertically, rather than horizontally ie on a product-by-product basis. At the same time there must be in existence credible, independent third party committees which review and pass judgment on all tests and experiments to be carried out in the UK. The UK has an Advisory Committee System for regulating biotechnology but certainly as fas as Ciba is concerned this system does not have a very high profile. The system is represented by the Advisory Committee for Genetic Modification (ACGM), Release into the Environment (ACRE) and Novel Foods and Processes (ACNFP).

CONCLUSION

Ciba, like all global companies has to attract management talent and scientific talent in the countries in which it operates to run and grow the company world-wide. Such talent is certainly to be found at the moment in the UK and exploitation of that talent through inward investment is a matter of ongoing policy. At present Ciba employs in the UK in all its Divisions some 5,700 people. Clearly such investment is a benefit to the UK economy. It brings jobs and helps to keep the industrial and academic communities at the forefront of modern technology of which biotechnology will continue to form a significant part. However, if the cost of this inward investment becomes relatively high in terms of money or time because of a need to satisfy bureaucratic demands or public opposition, then the investment is likely to be made elsewhere. Whilst no certain prediction can be made it appears that there may be a danger of this happening. The phrase "It's easier to do it (meaning biotechnology) in the USA" is frequently heard.

Evidence from the CBI

SUMMARY

- Biotechnology will bring major benefits to the UK balance of trade as products in a range of sectors begin commercialisation. These sectors include health care, agriculture, food and drink, environmental clean-up and fine chemicals. The UK has strengths in the life sciences within its universities, and industrial laboratories which provide the base for biotechnology to expand.
- However, because the commercial products of biotechnology vary considerably, a sector-based approach to regulation is preferred with products judged on their safety, quality and efficacy rather than the technology used in their production.
- The regulatory climate is crucial in dictating whether companies based in the UK can compete globally. Process (horizontal) regulation that is based on how a product is made rather than the end product itself will weaken the competitiveness of companies because US and Japanese systems—based on product legislation—appear more flexible. There is therefore a need to reassess the EC Directives 219 and 220, which impose process-based regulations on member states.
- Aside from regulation of the technology, the protection of intellectual property, and labelling issues need to be resolved to dispel the uncertainty hanging over regulation of biotechnology in Europe.
- Public perception will dictate the long term ability of companies to sell products, especially in the agricultural, and food and drink sectors. Greater public understanding of biotechnology, science and industry is part of the answer which requires efforts from both industry and government.
- As well as regulating biotechnology, government has a key role to play in promoting and championing it. Up to now activities have lacked co-ordination and focus.

1. *What is your interest in biotechnology?*

CBI formed a Genetic Engineering Working Party in 1979 in response to UK based companies' requests for industrial representation on matters relating to biotechnology (mainly genetic modification and cell fusion and culture). This name was later changed to the Biotechnology Working Party (extant) to reflect the broad spread of companies and associations in membership.

The Working Party promotes the pan-industry view to government and opinion formers on issues affecting the industrial development and exploitation of genetic modification and other biotechnology techniques. While recognising that sector oganisations are better placed to deal with matters affecting the core activities of their members, CBI's role is to coordinate policy and provide a network and forum for an exchange of views. Membership includes the main trade associations as well as several leading UK based pharmaceutical, brewing and agricultural firms, and a number of smaller companies (a list of members is appended).

As the major employers' organisation, CBI nominates three professional expert industrialists to the Health and Safety Commission's Advisory Committee on Genetic Modification (ACGM), and expert representatives to the Department of the Environment's Advisory Committee on Releases into the Environment (ACRE).

2. *How and why is biotechnology important to UK industry?*

CBI's report in 1992, "Making it in Britain" highlighted the importance of an internationally competitive manufacturing base to provide wealth, investment and employment on a sustainable basis.

Biotechnology is being increasingly used by a range of sectors that form the bedrock of the UK manufacturing base, including pharmaceuticals and health care, food and drink, agriculture, and chemicals. There are also spin-offs into scientific instrumentation, fermentation and laboratory equipment, as well as processing equipment.

Biotechnology is providing the tools for these sectors to be more productive and to generate novel, safe products of high quality—essential for competing in global markets.

Biotechnology products are already improving the quality of life of thousands of people in the UK. New forms of human insulin, growth hormones, vaccines etc are already available. Agricultural products such as pest-resistant crops and novel biocides which can dramatically reduce the need for chemical pesticide inputs are also nearing the market.

Since the UK's competitors in these same sectors have also adopted biotechnology techniques in research, development, production and processing, it is essential for the competitiveness of UK-based companies that they can operate on equal terms.

Biotechnology sales in the UK were estimated at $650 million in 1991 (Burril and Roberts), compared to $4,000 million in the US. By the year 2000 estimates of over $100 billion world-wide have been predicted. The UK has the opportunity to seize an increasing share of this which would accrue massive benefits to its economy.

3. *What future prospects and opportunities does the technology offer?*

Several recent reports by NEDO (1991), ACOST (1990) and BJAB (1991) have tackled this question in depth, and CBI would not disagree with many of the conclusions and recommendations. A broader analysis has also been conducted by OECD (1989).

The prospects are immense—the understanding of genetics and molecular biology which are at the core of biotechnology—are indispensable to our understanding of all biological processes from cancer or AIDS on the one hand and photosynthesis or fermentation on the other. The UK is well placed to build on this core understanding with its strong tradition of life science research in its universities, institutes and industrial laboratories.

4. *Which developments in biotechnology raise safety issues and how should they be addressed?*

Industry accepts the need for regulation and has argued that this should be firmly built on scientific principles, and related to the known risks.

It is implicit that risks need to be assessed in relation to both human health and safety, and the environment. But while risk assessment is key, it in turn should be dependent on the type of organisms being handled, whether viruses, bacteria, plants etc. Precautions should reflect the degree of uncertainty, with development of regulations as knowledge develops. This approach—on a case-by-case basis allied to risk assessment and monitoring—is likely to instil public confidence. The advisory system in the UK involving ACGM and ACRE, and ACNFP (Advisory Committee on Novel Foods and Processes)—has essentially followed this approach, and CBI believes this has worked extremely well. Indeed, the safety record in the UK—both in terms of human health and environmental safety—over the past 20 years has been exemplary.

5. *Should biotechnology be regulated by an industry specific regime?*

There is a difficulty in defining the biotechnology industry. While there are areas of common interest for firms using biotechnology there is also a great deal of diversity in the products these companies make. A majority of companies want their products to be judged on the requirements of safety, efficacy, and quality using existing sectoral legislation which may develop as necessary in the light of experience. Essentially, there are clear dividing lines between health care products such as vaccines and new crops or industrial enzymes. Attempting blanket regulations leads to major problems of scope-setting and definition which are the basis of concerns over EC Directives 219 and 220.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

The general view of members of the CBI's Biotechnology Working is that a product should be judged on the three criteria of safety, efficacy, and quality, irrespective of how it is made. The use of genetic modification should not in itself be a reason for a product to follow a different regulatory path to one that has not been produced using genetic modification. There may be a case for a horizontal approach for the technology itself (as opposed to its resulting products) for example, in the research laboratory in order to protect human health and safety and the environment.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

In general terms there can be no rule for this. For biotechnology the principles outlined earlier of risk assessment based on scientific criteria should be applied, together with those of safety efficacy and quality. If these are met for a particular product, vertical regulations, based on sector, are to be preferred. However, there is concern that attempting to transpose the EC directives 219 and 220 from horizontal to vertical legislation would lead to problems.

8. *How do current regulations compare with those of other competitor countries*

- *in Europe*
- *in the Far East*
- *the USA?*

In Europe, implementation of the Directives 219 and 220 is patchy, with only the UK, Denmark, Germany and the Netherlands reported to have implemented. This is despite the Commission's deadline of the end of October 1991. This delay is undoubtedly due in part to the extremely complex nature of the Directives. It is therefore difficult to compare, and although in theory national implementation of Directives should create a "level playing field", differences in interpretation and enforcement make this unlikely.

The approach of the US administration, under ex-President Bush's Council on Competitiveness, outlined four principles of regulatory review. The first, relating to safety states the following:

> *"Federal Government regulatory oversight should focus on the characteristics of the biotechnology product—not the process by which it is created.*
>
> *Products developed through biotechnology do not per se pose risks to human health and the environment; risks depend on the characteristics and the use of individual products. Biotechnology products that pose little or no risk should not be subject to unnecessary regulatory review during testing and commercialisation. This allows agencies to concentrate resources in areas that may pose substantial risks and leaves relatively unfettered the development of biotechnology products posing little or no risk."*

This overiding principle of product rather than process assessment, with political backing at the highest levels, contrasts with the approach adopted in Europe under EC Directives 219 and 220, and recently implemented in the UK.

The product-based approach of the US allows for "fast-tracking" where the perceived risks are negligible. Recently, the United States Department of Agriculture has moved towards a notification only procedure for around six major crops. In the UK an authorisation is required before any crop can be introduced into the environment, for which a charge is made.

In Japan, a system based on guidelines is in operation.

Individual companies are best placed to provide direct experience of operating in these markets.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards*

(1) research
(2) product development
(3) investment
(4) location
(5) sales and marketing?

Most companies using biotechnology are competing in global markets and have subsidiaries in many parts of the world. Consequently, when the climate to carry out any of the above is perceived to be less favourable, they are able, if need be, to move their activities to other locations. There is a risk that as a result of higher costs arising from new legislation in the UK that the options for relocations will be seriously considered. Recent surveys indicate that Europe as a whole is perceived as a less favourable environment than, for example, the US and Japan. This is not helped by the overall air of regulatory uncertainty in relation to patenting, food labelling and the inevitably slow procedures for redressing current regulatory problems.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

Universities in the UK are working to very tight budgets, but unlike industry, they are unable relocate to continue the work. The danger is that key researchers will move instead, or that departments will move away from research that is too costly or requires excessive paperwork and administration to conduct. This could affect the flow of experienced graduates and postgraduates into UK-based industry. Equally, should companies move out of the UK on a large scale this could limit sources of industrial funding to university departments.

11. *How best can issues of public acceptance be addressed?*

This issue encompasses the wider problem of the public understanding of science and industry. The public must be reassured that products are safe and can provide benefits, whether the products are novel pharmaceuticals or vegetables. Appropriate legislation is one essential component for ensuring public acceptance, though it does not necessarily ensure public understanding.

Acceptance is more likely to be achieved if it follows from a balanced understanding of the issues, the technology, and the end products. Ensuring that school teachers are kept up to date on new developments in biology, promoted in a balanced way to pupils, is one key element. But the need to educate, inform and promote the benefits arising from each biotechnology sector to the wider public is also crucial. Both government and industry have responsibilities here although the conclusion from BJAB (1991) that . . . *"there is a strong case for publicly-funded initiatives to improve public perception; they should be distanced from company activity, and should concentrate on the provision of objective, independent and authoritative information"* is strongly supported. The approach from government departments has been relatively unsystematic and uncoordinated, and though there are several departments active in regulating biotechnology, led by the Department of the Environment, there is no equivalent "champion" with a clear remit to promote biotechnology.

However, there is also a strong case for improving the coordination of activities by industry as it is recognised that companies themselves must be responsible for marketing and ultimately convincing retailers to stock products on their shelves for the public to purchase.

The greatest hurdles to public acceptance in the future are likely to arise for food and drink products and it is here that dialogue between government, industry and responsible pressure groups could yield valuable consensus.

Ethical issues cannot be ignored and should be handled with sensitivity on a case by case basis, though unfortunately the issues are frequently confused and sensationalised. For example the public need to understand the difference between somatic gene therapy (where changes are not heritable) and germline manipulation (where there is an accepted moratorium on humans), or between genetic modification and traditional hybridisation in crops, where the latter often creates a great deal more genetic variability.

The Nuffield Committee on Bioethics provides a useful role in providing ethical oversight.

The influence of the media is also crucial and it is industry's role to ensure that inaccurate and damaging coverage by reporters, television producers, editors etc is challenged.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

Intellectual Property Rights

Companies developing biotechnology products in the EC will only continue to invest if they can be sure of protecting their ideas. Therefore, legal protection of intellectual property in the biotechnology field is essential. The proposed EC Directive on the Protection of Biotechnological Inventions, has been welcomed as a move towards harmonising patent rules in EC member states, though recent amendments proposed by the European Parliament may weaken the initiative and potentially deter companies from patenting in the EC. In particular companies are concerned about the precedent set by the farmer's privilege and compulsory licencing clauses. The European Patent Office has recently granted a number of broad patent claims which many companies believe are not justifiable and could restrict future work.

These developments add to the air of regulatory uncertainty.

Labelling of Consumer Products

While companies are not against labelling that helps inform the consumer, labelling of food or drink products where genetic modification has been used, must be given careful consideration: the important factors of safety wholesomeness and quality must not be overshadowed by any alarm due to lack of understanding of the wording used.

Government coordination

While the Department of the Environment leads on legislation relating to genetic modification there are a number of other departments with a significant interest including Employment (via the Health and Safety Executive), MAFF, Office of Science and Technology, Department of Health, and the DTI. The recent establishment of BIGRAG is an important move to ensure better coordination, though it remains the case that government departments lack a clear remit to promote biotechnology, or provide balanced information for the public at large.

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NEDO—New Life for Industry—Biotechnology, industry and the community in the 1990s and beyond. NEDC 1991

OECD 1986—Recombinant DNA Safety Considerations
OECD 1988—Biotechnology and the changing role of Government
OECD 1989—Biotechnology—Economic and wider impacts

US President's Council on Competitiveness—Report on National Biotechnology Policy—February 1991.

Companies and Organisations in the CBI Biotechnology Working Party

British Bio-Technology Ltd

Agricultural Genetics Co Ltd

British Society of Plant Breeders Ltd

Pfizer Ltd

McKenna & Co

WRC Plc

BioIndustry Association

The Brewers Society

Food & Drink Federation

Association of British Pharmaceutical Industry

ICI Plc

British Agrochemicals Association Ltd

SmithKline Beecham Pharmaceuticals

Unilever Research

Chemical Industries Association Ltd

Pig Improvement Company Ltd

Glaxo Group Research Ltd

Zeneca Seeds

Zeneca Pharmaceuticals

Letter to the Clerk from Dr Yvonne Cripps, Director of Studies in Law, Emmanuel College, Cambridge

Thank you for your letter of 19 February 1993. I respond below to the questions on which you invited evidence.

1. I have been interested in biotechnology since the mid 1970s when, though a non-scientist, I read about developments in this field in scientific journals such as New Scientist and Nature. I later went on to qualify as

a lawyer and then to an academic career in law, maintaining my interest in the area. I have acted as a consultant on the legal implications of biotechnology to the Royal Commission on Environmental Pollution (working with Lords Lewis and Nathan), the New Zealand Ministry of Health, the Genetics Department of the University of Cambridge, the Stockholm Environment Institute, the Biology Department of the University of York and Chiros Ltd (a company which manufactures genetically modified pharmaceuticals). I teach courses on intellectual property law and biotechnology law at the University of Cambridge and at Cornell University. I am also a co-editor of the Biotechnology Law Report—a journal devoted principally to the intellectual property implications of biotechnology and published monthly in New York.

2. The term "biotechnology" normally encompasses not only genetic modification by means of splicing genetic material but also more traditional processes such as those involved in brewing and cheese making. I shall focus mainly on the newer techniques of splicing. I believe that biotechnology is extremely important to United Kingdom industry because, *inter alia,* it facilitates the rapid production of large quantities of hitherto scarce commodities such as human insulin and certain other hormones, lowering prices and increasing supply and competitiveness. In addition, various diagnostic kits as well as new pharmaceuticals and vaccines have reached the market. Biotechnology also has important implications for agriculture and the food industry with several pesticides based on naturally occurring viruses now commercially available. Strains of the bacterium *Rhizobium* are sold in place of fertilisers in order to improve the uptake of nitrogen from the soil. Genetically modified food products are on sale both in the United Kingdom and abroad. The world's first patent on a genetically modified organism was granted in 1976 in the United Kingdom. The organism to which the patent relates is a genetically modified oil consuming *Pseudomonas* bacterium which plays a part in pollution control.

3. The future for biotechnology looks very promising indeed. Work is well advanced on the production of pest and herbicide resistant plants. Further developments in food processing and enhancing crop yields and quality are confidently expected. There also appears to be reason to be optimistic that certain cancers will be cured by human gene therapy. Terminaly ill cancer patients in the United States have recently received gene therapy and the first British human gene therapy occurred this month when treatment was commenced on an infant who has a congenital condition that leaves her without resistance to infection. (The trial was approved by the Clothier Committee on 11 March 1993). Much gene therapy is focused on replacement of defective genes and this technique has proved successful in the United States in the treatment of defects which, for example, prevent the immune system from producing the enzyme adenosine deaminase. There is also evidence that cystic fibrosis and muscular dystrophy may eventually be curable by gene therapy.

4. I believe that significant steps have already been taken to regulate the safety of biotechnology and that these steps should be drawn to the attention of the public to allay fears that are well grounded as well as those which, perhaps more commonly, arise from lack of knowledge not only about regulatory measures already in place but also from lack of knowledge about the techniques themselves. If one focuses on gene splicing as opposed to more traditional biotechnological techniques such as fermentation and selective breeding, there are two broad areas of interest in relation to safety. The first involves the contained use of genetically modified organisms and the second the deliberate release of such organisms to the environment (I use organism somewhat loosely to encompass viruses).

The Genetically Modified Organisms (Contained Use) Regulations 1992 (SI 1992/3217) were promulgated under the Health and Safety at Work Act 1974 and the European Communities Act 1972 to facilitate the safe contained use and handling of genetically modified organisms. They came into force on 1 February 1993 and repeal and replace the Genetic Manipulation Regulations 1989. They implement EC Directive 90/219/EEC (OJ L117, 8 May 1990, 1). The Advisory Committee on Genetic Modification (ACGM) advises the Health and Safety Executive and relevant Ministers on decisions under the legislation. The contained use regulations apply in different ways to genetically modified micro-organisms and organisms. In the case of micro-organisms, risks to human health and the wider environment are covered, whereas in the case of work with organisms, such as plants and animals, only human health is covered. Environmental risks relating to organisms are covered by section 108(1)(a) of the Environmental Protection Act 1990 which relates to risk assessment and notification requirements as elaborated upon in the Genetically Modified Organisms (Contained Use) Regulations 1993 (SI 1993/15). The regulations of 1993 provide, *inter alia,* for certain exceptions to section 108(1)(a). Section 109 of the Environmental Protection Act places on persons proposing to import, acquire or release genetically modified organisms civil law duties of care relating to risks of environmental damage.

The Genetically Modified Organisms (Deliberate Release) Regulations 1992 (SI 1992/3280) were promulgated under the Environmental Protection Act 1990 and the European Communities Act 1972. They came into force on 1 February 1993 and implement EC Directive 90/220/EEC (OJ L117, 8 May 1990, 15). These regulations elaborate upon the provisions of Part VI of the Environmental Protection Act 1990 which relate to the escape and release of genetically modified organisms to the environment. In essence the Act requires those keeping, acquiring, importing, releasing and marketing genetically modified organisms to carry out a risk assessment of possible damage to the environment. The Secretary of State may prohibit certain activities and formal consents must be obtained from him. Provision was also made in the Act for public registers of information relating to genetically modified organisms. The Advisory Committee on Releases to the Environment (ACRE) was appointed under the Act to advise the Secretary of State. Section 109(3)(c) of the Environmental Protection Act requires those involved with genetically modified organisms to use the best available techniques not involving excessive cost (BATNEEC) for keeping the genetically modified organisms under control and preventing damage to the environment. (See the 14th Report of the Royal Commission on Environmental Pollution, Cm. 1557).

The Health and Safety at Work Act, the Environment Protection Act and the regulations outlined above are not the only legislative provisions relating to genetically modified organisms. Other relevant statutes include the Control of Substances Hazardous to Health Regulations 1988; the Medicines Acts 1968 and 1971 (human and veterinary medicines); the Animals (Scientific Procedures) Act 1986 (transgenic animals); the Food and Environment Protection Act 1985 (pesticides); the Plant Health (Great Britain) Order 1987 (plant pathogens and genetically modified plants and plant material); the Wildlife and Countryside Act 1981 (introduction of novel species) and the Consumer Protection Act 1987.

In my view the legislation currently in place in the UK addresses issues of safety in as thorough a fashion as can be hoped for if British biotechnology is to remain competitive.

5. As indicated in my response to question 4, biotechnology is regulated by a combination of industry specific measures and measures with a broader compass. (I use "industry specific" here to refer to regulation of work with genetically modified organisms as opposed to legislation designed to deal with less specific issues concerning, for example, health or the environment. In my response to question 6 I refer to vertical regulation in terms of regulation aimed at particular products rather than at genetic modification in general.) I believe that biotechnology should continue to be regulated by specific and less than specific regimes. Certain unique features of the technology such as the speed with which significant genetic alterations may be achieved require special regulatory attention. But this does not suggest that biotechnology should be regulated by only one specific Act with accompanying regulations. Many of the issues that arise in relation to biotechnology also arise elsewhere and public confidence might be dented if biotechnology were excluded from legislation that would otherwise cover it, even if such exclusions were in the name of regulating the technology with a single comprehensive statute and accompanying regulations. Yet it might be argued that the public would be reassured if all the separate provisions currently applying to biotechnology were drawn together in a single statute with accompanying regulations. On balance I prefer the existing mixture of industry specific and other regimes despite the consequent fragmentation of jurisdiction and enforcement.

6. Although I am not a scientist, I believe that biotechnology requires, as at present, a combination of horizontal and vertical regulation. The processes of genetic modification may be highly focused as where enzymes are used to "cut" genetic material, or extremely lacking in specificity as in the case of the so-called "shotgun" techniques. It may be important to control some processes more rigorously than others. The products of biotechnology are even more various—some, for example, being more virulent and enduring than others. At least at present horizontal and vertical regulation seems desirable.

7. It would not be surprising if, as expertise and experience increases, the regulatory process shifts further towards a vertical approach which would place greater emphasis on the characteristics of a genetically modified product rather than on the process by which it was created. Categories of genetically modified product deemed to be of insignificant risk will no doubt be developed and refined. Indeed this has to some extent occurred already in that ACRE and ACGM already use streamlined procedures (all consultation is postal in these cases) to advise upon certain types of application. Where the streamlined procedure is used a reply on an application for consent to release can be given well within the prescribed 90 day period and the fee charged to an applicant is a quarter of the standard fee (£450 instead of £1,800—there is also an annual charge of £270 in each case). The equivalent figures where there is an application for consent to market are 150 days, £2,900 standard and £1,700 streamlined.

8. The European Community achieves Community wide control through its contained use and deliberate release Directives. The UK, France and Belgium are lobbying for more streamlined or simplified procedures at the Community level and it is hoped that these will be in place by the end of 1993. The current European time scale is 90 days in the case of applications for consent to release and 150 days in the case of applications for consent to market. Member states may, within the prescribed time scales, object to an application from another member state and if the matter cannot be resolved a qualified majority vote will be taken which then binds the other member states.

In the USA control is achieved through a variety of legislative measures and a set of National Institutes of Health Guidelines—the latter relating solely to work undertaken in the public sector. The degree of fragmentation in terms of the diverse mechanisms for regulation and enforcement is even greater than in the UK but the system for granting consent to releases focuses much more on the organism than the process by which it was created and is thus more vertical than our own. The FDA deals, *inter alia*, with modified veterinary, pharmaceutical and food products while the USDA controls, *inter alia*, modified crops and pesticides. Less information is also required by the APHIS (Animal and Plant Health Inspection Service) Form 2000. It contains approximately 13 questions as opposed to the release application form in the UK, which, in following the requirements set out in the Schedule of the Community release Directive, contains 89 questions. The possibility of the USDA moving to a system of notification as opposed to consent for releases is currently being mooted—if such a system were adopted that could give the US a distinct competitive advantage over the UK. The UK already operates a notification system in the sphere of contained use.

The Japanese system is much more flexible than that in either the UK or the US. This raises issues about our ability to compete with Japan although the Japanese government is currently considering the possibility of introducing legislation on genetically modified organisms. At present it only has guidelines and these guidelines are extremely sectoral or vertical. There are, for example, different guidelines for agriculture, drugs, science, and education.

Although it has no regulatory authority, the OECD continues to work towards international harmonisation of regulatory standards relating to biotechnology.

9. By February of this year approximately 70 applications for deliberate release had been made but there are currently approximately 5,000 contained use projects. It is likely that deliberate release applications will increase as some of the products developed in conditions of contained use move towards the marketing stage. The regulatory regime may slightly delay research and product development but the experience with the regime has perhaps been as positive as could have been expected in that the ACGM and ACRE have proved highly efficient. Industry would, however, like cheaper and more streamlined procedures and it is not impossible that the regulatory system prevailing in this country might cause industrialists to locate their enterprises in other jurisdictions, notably in developing countries where regulation is minimal or non existent. Yet with the exception of Japan our major competitors have controls which are not very significantly less difficult to comply with than our own. It is hard to imagine that it would be advisable for the UK to strip away safeguards to such a degree as to be on a regulatory par with countries in which there are no or few safeguards in respect of biotechnology and which tend to adopt a similarly lax attitude towards other industries, such as the chemical industry, which we choose to regulate. But at the same time some movement towards more streamlined procedures in certain cases could well be beneficial to the competitiveness of UK industry without jeopardising safety.

With regard to investment, it might, as a subsidiary point, be argued that investors will be drawn to those countries where well thought out regulations are in place as it will be easier to insure against liability for losses caused by the technology in those countries. This may be a factor to be taken into account by investors but at least at present it is unlikely to be a significant factor because it is virtually impossible to find insurers who will provide cover in this field. Not even the prospect of extremely high premiums has yet seemed sufficient to lure insurers into this area.

Those countries that have made sensible regulatory provision will, I suspect, be in a strong position with regard to sales and marketing because public confidence in products may well reflect the stringency of regulations and a consequent reduction in the chance of mishap, thus helping to promote a receptive market.

10. I believe that the regulations in place in the UK are efficiently administered and do not place undue burdens on the exploitation by British industry of research conducted in the UK science base. (In September of last year the Office of Science and Technology published a report entitled "Intellectual Property in the Public Sector Research Base" which may be of general interest to the Select Committee).

By placing much of the technical detail of control in regulations promulgated under a broadly framed empowering Act the legislature has, in my opinion, provided a means by which the UK can adjust the regulatory position rapidly as expertise with the relevant techniques increases along with knowledge of their risks.

Intellectual property law has a crucial role to play in the exploitation by British industry of research in this fast developing area especially if the United Kingdom is to maintain its competitiveness with other nations. As mentioned above, the UK led the world in the patenting of genetically engineered microorganisms and Harvard University's so called "onco-mouse" has been patented under the European Patent regime as well as in the United States. There is a European Community draft Directive on the "Legal Protection of Biotechnological Inventions". There is also a system of plant variety rights operating at the domestic and international levels (the European Community has also published a draft Community Breeders' Rights Regulation) although there is no equivalent system of animal variety rights—the patent system alone being available in that latter area.

Industry may well feel that it would suffer a set-back if agreement were reached on the amended draft "Biotechnological Inventions" Directive, with its provisions on farmers' privilege and dependency licences. These issues need to be handled with great care to ensure that the Community does not lose its competitive edge in the crucial sphere of intellectual property protection for biotechnical inventions.

Patents can only be granted on inventions which, *inter alia,* meet a test of "novelty". If information about an invention is, broadly speaking, in the public domain before an application is made for a patent it will fail the novelty test. In return for the patent rights the inventor discloses to the public information about the invention. As was pointed out during the debate of the Commons Third Standing Committee on Statutory Instruments on the contained use and deliberate release regulations (11 February 1993), the contained use regulations permit information to be excluded from the register if "it is necessary to withhold, for the time being, certain of the information . . . to protect . . . intellectual property rights." Since the Contained use Directive states that "in no case may the . . . information . . . be kept confidential" the crucial regulatory words in terms of reconciliation of the meaning of these provisions are "for the time being".

Most products require a lengthy period of testing before an application for approval is made to a regulatory committee. In the inorganic chemicals industry, for example, a patent application will normally be filed before a product approval application but after many trials have been conducted. If a genetically modified organism is to be released to the environment information is made available to the public under the regulatory regime at the stage of trial release. It might thus be thought necessary to file a patent application before the beginning of trials and this of course has implications for industry. This issue of the relationship between the requirement for public registers of information under the release Directive and the need to maintain commercial confidentiality or obtain a patent has been handled sensitively by DOE and ACRE which require less information for the register in cases where patents have not yet been applied for and the application is for release falling short of marketing. In these cases only a general description of the genetically modified organism along with the location and purpose of its release is required for the register. This is in accordance with Article 19 of the release Directive which states that "the competent authorities shall not divulge to third parties any confidential information . . . and shall protect intellectual property rights". The Secretary of State's approach may have a slight tendency to encourage industry to maintain confidentiality in the long term (thereby keeping details of their invention from competitors and others who might build upon it) in preference to protecting it with a patent. But the alternative of requiring full disclosure could, as suggested above, result in those seeking patent protection going through the costly process of applying for a patent even before the experimental trial stage. A decision given in 1991 by the Law Lords in the Asahi case might by analogy be called in aid to resolve this difficulty.

11. It is in my opinion crucially important that issues of public acceptance are addressed as effectively as possible as soon as possible. Industry might be encouraged to do more in this respect than it has so far seemed willing to do in terms of putting forward its genuinely powerful case for biotechnology. The existing and potential benefits of this technology need to be explained to the public so that they can appreciate the benefits which it can bring them. Those emphasising the risks of the technology have, in some ways been far more professional in their exploitation of the means of putting their side of the debate before the public. Survey evidence suggests there is a perception in the minds of a substantial majority of the general public that the technology is dangerous. Industry is very ill advised simply to vilify its opponents as "environmental extremists" and hope that that will be sufficient. It must engage in the debate rather than dismissing it and must make much more of what biotechnology can do for the consumer.

The regulatory regime which has recently been put into place in the UK is extremely thorough and precautionary and no proponent of biotechnology need fear allegations that biotechnology is insufficiently regulated in this country. That factor should also be brought out in response to allegations about the risks of biotechnology although heavy emphasis on the stringency of the regulatory regime might entrench the existing public perception of significant risk, or even foster it in some cases in place of previous lack of strong feeling on this issue. One of the most important features of the regulatory regime in terms of public attitude is that the regime is likely to prevent accidents. Even a single accident could produce a tremendous decline in public confidence in biotechnology especially amongst a public yet convinced of the benefits which the technology can bring.

Secrecy about biotechnology should be kept to an absolute minimum, *inter alia,* because secrecy is likely to enhance the public's perception that industry and researhers have something that would engender public disapproval to hide. Again it seems to me that care has been taken by the framers of the regulatory regimes to avoid unnecessary secrecy. Note also the Environmental Information Regulations 1992 which are designed to facilitate the public's access to information about matters affecting the environment. In additon to the requirements for public registers relating to contained use and deliberate release, there is a requirement in regulation 8 of the release regulations that applicants for consent to release must, between 14 and 28 days of receiving an acknowledgement from the Secretary of State of receipt of the application, advertise in a local newspaper their name and address, a general description of the organisms to be released, the location and general purpose of the release and the foreseen dates of the release. This advertisement will therefore be placed before consent is given. With regard to the registers of information, it is interesting to note that applicants arguments as to why there should be confidentiality in certain cases are not currently included in the register.

12. In addition to the amended draft Directive on the Legal Protection of Biotechnological Inventions, to which I have referred above, there is also a draft Community Breeders' Rights Regulation which could seriously affect the interests of plant breeders in this country. It is also important to note that a trans-Atlantic battle is currently being waged for patents over certain nucleotide sequences of the human genome. Scientists in the UK are forced by considerations of competitiveness to take part in this battle although they are quite united in the belief that the relevant fragments should not be patented, preferring to see the fragments treated as discoveries rather than patentable inventions, with only *modified* organisms falling into the category of inventions. In other words it is felt that the isolated sequences should not in themselves be patentable thus leaving all researchers free to work on the sequences to produce truly novel entities which would then be patentable if the other relevant criteria of patentability were met. The UK is extremely well placed to continue its role in inventing novel micro-organisms and organisms and Britain's position was enhanced earlier this month when an £8 million joint bid by the MRC and the Wellcombe Trust to bring the European Bioinformatics Institute from Heidelberg to Hinxton was accepted by the European Molecular Biology Laboratory. This will further increase research activity in the UK and is likely to attract additional investment in the British biotechnology industry.

I hope that these comments will be of some assistance to the Select Committee.

Yvonne Cripps

Evidence from Professor J E Dale, Division of Biological Sciences, The University of Edinburgh

1. *Interest in Biotechnology*

Edinburgh University is involved in the teaching of courses relevant to Biotechnology and many of the research projects conducted in the Faculties of Science and Engineering, Medicine and Veterinary Medicine interface with biotechnology and its enabling disciplines.

2. *Importance of Biotechnology to UK Industry*

UK has particular strength in the pharmaceutical, health care and agricultural industries. The role of biotechnology in producing new products in these particular areas is paramount. UK has expertise in many of the disciplines required for new developments and products.

3. *Future Prospects and Opportunities offered by Biotechnology*

In many areas such as vaccine development, improved diagnostic procedures, gene therapy, new antimicrobial agents, etc. Biotechnology offers rapid and novel advances. Some of these offer good prospects for commercial success.

4. *Which developments raise issues of safety*

There is an innate fear of "genetically engineered micro-organisms and plants, etc." and the public requires assurance that all developments incorporate safety checks and that products are inherently safe.

5.–7. *No comment*

8. *How do current regulations compare with those of competitor countries*

In Europe, the UK regulations are comparable with those in the Netherlands and in Denmark—countries with similar biotechnological interests. They are less restrictive than those in Germany and Switzerland where current legal restrictions have greatly hindered biotechnological developments. It is unclear what the situation in the eastern European countries is.

In the Far East, certain regulations are less restrictive (eg those involving food) while others appear to be similar to those in the UK and the US.

9. *What are the consequences of the regulatory regime on competitiveness?*

Research is likely to be greatly inhibited by certain proposed schemes for regulation. This is especially true if regulation requires expensive annual schemes for recertification at the University or research institute level at which many projects are initiated.

Product development is less likely to suffer but again may well be inhibited by highly restrictive regulations.

10. *Prevention of exploitation*

Despite fears about possible restrictiveness, the present UK regulatory scheme *appears to work reasonably well*. There is a need for an effective dialogue involving all parties—universities, research institutes, industry and government—at all stages when regulation is changed or developed.

11. *Public acceptance*

While the UK has not so far had to suffer from the antagonism seen in Germany or the Netherlands or by the Jerry Rifkinds of the US, acceptance cannot be taken for granted. The COPUS scheme of the Royal Society and similar mechanisms using knowledgeable and excellent communicators is essential and should if possible be extended. The OST should be strengthened and Government made more aware of the problems and potential of the Biotechnology Industry.

12. *Other Factors*

It is essential that the UK has a core of highly trained and adequately financed reseachers capable of initiating the enabling research. The current lack of financial support at the University level and lack of a career structure which will attract and retain the best of our young scientists in the enabling disciplines bodes ill for the future of UK Biotechnology. Small companies with good product potential also require a financial regime which will enable them to take their products to the market as well as the support of Local Enterprise Companies to assist in marketing, development advice, etc.

Evidence from Denton Hall Burgin & Warrens

Executive Summary

- Few would question the need for regulation of the biotechnology industry; differences of opinion appear in the degree and manner of regulation.
- Member States within the EC have historically taken inconsistent approaches. The Commission wishes to harmonize, to prevent barriers to trade.
- The approach of the Commission has been inconsistent: certain policy statements and established principles of EC law suggest it is aware of the need to preserve competitiveness and flexibility by not over-regulating. However some measures actually enacted and the stated philosophy behind them, have followed an approach (horizontal) which in our view militates against competitiveness.
- An illustration of the dangers of allowing horizontal legislation to grow up without due thought to the practical consequences is found in measures (both existing and proposed) relating to biotechnology and the food industry. There we submit the UK has quite adequate controls imposed by the Food Safety Act 1990 and the Consumer Protection Act 1987 in the event of food not meeting safety requirements.
- We have identified situations in the UK where the marketing of food containing genetically modified organisms, even if it fully complies with the safety requirements established by these two Acts, would have to comply with three separate layers of horizontal regulation in addition, before such food could be sold.
- The global competitiveness of the UK (and EC) biotechnology industry is likely to be severely weakened if such an approach becomes dominant: the USA for example, clearly has recognized the need to avoid over-regulating its biotechnology industry.

1. *Introduction*

1.1 Denton Hall Burgin & Warrens ("Denton Hall") thanks the Chairman and Sub-Committee II of the House of Lords Select Committee on Science and Technology for this opportunity to submit written evidence.

1.2 Our interest in biotechnology derives from our role as legal advisers to clients at all levels in the industry. As one of the largest firms of solicitors in the UK we act for a variety of UK and overseas clients in the biotechnology area, from those engaged in primary research through to manufacturers and retailers. Whilst we do not feel qualified to submit evidence on all the questions enclosed with the Chief Clerk's letter of 19th February 1993, we feel we can make a useful contribution on the issues raised by question 6, namely whether "horizontal" or "vertical" regulation of the industry is preferable.

2. *The need for Regulation in the Biotechnology industry*

2.1 The application of biotechnological techniques to existing scientific and industrial activities has enormous implications on scientific, commercial and ethical levels. Given the very novelty of what can be done with biotechnology, few could question the need for a framework of regulation to ensure such activities are safe.

2.2 There is however no such consensus as to the form and extent of such regulation, and this is due to the tension between several competing considerations. For example:

- Scientific: tension between the ends which might be achieved if certain biotechnological activities are carried out, and the dangers to humans or the environment which the means to reach them may create;
- Commercial: tension between the aims of national governments and the EC on the one hand to lay down effective safeguards, and on the other hand to prevent imposing an unnecessary burden of regulatory compliance on industry, diminishing competitiveness;
- Ethical: tension between those who object to any "unnatural" manipulation of genetic structures and those who regard this as part of the progress of human understanding.

3. *Differing Approaches to regulation*

3.1 Whether a "horizontal" or a "vertical" approach to regulation is adopted, is influenced heavily by the interplay of these tensions. In an industry as young as biotechnology, it is hardly surprising that different countries have adopted different approaches. The UK has (as discussed further below) tended to favour a "vertical" approach, whilst Denmark for example, with the very strict controls laid down under its Environmental and Gene Technology Act 1986, has favoured the "horizontal" approach.

3.2 In Order to prevent these different regimes creating barriers to trade between member states, the European Community has clearly targeted the biotechnology industry for harmonisation, and has passed, or proposes to pass, various measures to ensure this.

3.3 However we submit that the approach of Brussels to these measures has been inconsistent. On the one hand it is a well-established principle of EC law, going back to the *Cassis de Dijon* judgement, that legislation should follow "the principle of proportionality", that is that legislative measures must not go further than is generally necessary to achieve the desired objective. For example, this principle was noted with approval in the EC Communication entitled "Completion of the Internal Market: Community Legislation on Foodstuffs" (COM(85) 603 Final). That Communication also rejected the idea of a "recipe law" (ie, extremely detailed regulations on the composition and manufacturing characteristics of each food stuff) on the basis that "legislative rigidity concerning product composition prevents the development of new products and is therefore an obstacle to innovation and commercial flexibility".

3.4 On the other hand, we find the following in the recitals to the "General Product Safety Directive" (92/59/EEC):

> "Whereas some Member States have adopted horizontal legislation on product safety, imposing, in particular, a general obligation on economic operators to market only safe products; whereas . . . the absence of horizontal legislation in other Member States is liable to create barriers to trade and distortions of competition within the internal market.
>
> Whereas it is very difficult to adopt Community legislation for every product which exists or may be developed; whereas there is a need for a broadly based legislative framework of a horizontal nature to deal with those products, and also to cover lacunae in existing or forthcoming specific legislation, in particular with a view to ensuring a high level of protection of the safety and health of persons, as required by Article 100A(3) of the Treaty".

3.5 Moreover the general tenor of the new EC Novel Foods Regulation (which is discussed in more detail below) is very much of the "horizontal" type.

3.6 In our view if the horizontal trend is followed this will not assist the growth of the biotechnology industry within the EC, nor will it help the competitiveness of the global trading position of the Community as a whole. This contrasts with the more "vertical" approach adopted by the United States (see 6.1 below).

3.7 It appears that the Commission itself (or certain parts of it) is recognising shortcomings in over-emphasising the horizontal approach. The Commission's 1991 Policy Statement: "Promoting the competitive environment for the industrial activities based on biotechnology in the Community" (S.3/91) states:

> "The Community's public authorities are responsible for ensuring that the regulatory and industrial frameworks relating to biotechnology which exist in the Community are conducive to the competitive development of the industries involved... The Commission will ensure that the Community does not over-regulate and that the Community's legislation for biotechnology is coherent."

3.8 If this is genuinely going to be the EC's view in the future, we welcome this. However the Statement also seeks to bridge the inconsistency between horizontal and vertical regulation by suggesting that horizontal regulation should be made "full use of ... in order to guarantee that unknown risks are assessed at an early stage." The vertical approach should be used for specific sectors and products affected by biotechnology.

4. *Novel Foods*

4.1 By way of illustration of the above points, we propose to discuss in the remainder of this paper the current position in the UK on the regulation of novel foods created with the aid of biotechnological applications, and ancillary labelling requirements.

4.2 The primary legislation in the UK dealing with the safety of foods is the Food Safety Act 1990 ("the Food Safety Act"). This provides that it is a criminal offence to render food injurious to health (for example) by subjecting the food to some process or treatment. It is also an offence to sell food which does not comply with food safety requirements, which would include selling food rendered injurious to health by someone else, and selling food which is not of the nature, substance or quality demanded by the purchaser. The approach here is vertical: there are no provisions at present in the UK requiring the manufacturer or retailer to establish, to the satisfaction of a regulatory authority, the safety of a food product before its sale.

4.3 The Consumer Protection Act 1987, which implements the EC Product Liability Directive (85/374/EEC), is also applicable to food although not to food, like game or crops, which have not undergone an "industrial process". Where a product is defective and causes damage, including death or injury, a number of different parties are liable jointly for the damage, ie the producer, the retailer who attaches his own brand name, and the importer. Liability for breach is "strict"—ie it does not depend on showing fault. Between themselves the parties may be able to assign liability to the one party who is actually at fault. Again a vertical approach is taken: the Act does not require safety to be established before the product is sold, but imposes penalties if the food is subsequently determined as being unsafe

4.4 The EC Product Liability Directive implemented by the Consumer Protection Act 1987 will soon be supplemented by a Directive on General Product Safety (92/59/EEC) which is due to be introduced by all EC Member States before 30 June 1994. The Directive has the effect of extending the regulation of food by introducing a "general safety requirement" in respect of all food and not merely that food which has been subject to an industrial process protected by the Consumer Protection Act 1987.

4.5 (We have seen (3.4) that this Directive regards itself as adopting a "horizontal" approach. However, the use of the word "horizontal" in this Directive seems not to accord with the definition of that word in question 6 to which this paper is a response. The Directive is essentially concerned with the safety and characteristics of the end product as placed on the market. This indicates a "vertical" approach like that of the Food Safety and Consumer Protection Acts 1987, rather than a "horizontal" one. However, to discuss whether or not there is semantic inconsistency in the manner in which the words "horizontal" and "vertical" are used, lies beyond the scope of this paper. Whatever label is chosen the substantive issue remains whether regulation should primarily be concerned with the safety and characteristics of the end product or the processes which give rise to that end product).

4.6 Complementing the Food Safety and Consumer Protection Acts, there is currently in operation in the UK a voluntary clearance scheme operated by the Department of Health and the Department of Agriculture Fisheries and Food acting, on advice from an advisory panel (ie the Advisory Committee on Novel Foods and Processes), although there is no *obligation* on the producer of a novel food to inform the Advisory Committee on Novel Foods and Processes before placing the product on the market.

4.7 It might be argued that the approach of this UK legislation means there is a danger that unsafe products could be marketed and consumed freely, before any action were taken, and that such action would be in the nature of "shutting the stable door after the horse has bolted". However, our view is that the strict liability regime, together with the attendant adverse publicity which any conviction or liability would bring, acts as a very effective incentive to ensure compliance.

5. *The Novel Foods Regulation*

5.1 The Commission has published a proposed Regulation on Novel Foods (92/C 190/04). It adopts a "horizontal" approach, laying down two types of procedures to be followed when placing a food or ingredient on the market for the first time: a national procedure and a centralised procedure. As a general rule the national procedure will be followed, but where the food, when eaten, is a viable organism, that is to say capable of replication or of transferring genetic material (for example a modified fruit eaten raw), or where there is insufficient scientific data to demonstrate the safety of the food, then the centralised procedure must be followed.

5.2 The national procedure essentially requires notification to the Commission of an intention to market the product, together with a summary of the evidence that the product complies with certain general criteria and an opinion from an expert that this evidence is satisfactory. If the applicant hears nothing after three months he may place the product on the market. If he receives a negative opinion from the Commission within that time then the centralised procedure must be followed.

5.3 Under the centralised procedure, the applicant must send to the Commission a request for authorisation, accompanied by the information necessary to show satisfaction of the compliance criteria. The Commission will, after consultation with its Standing Committee on Foodstuffs, inform the applicant of its final decision which could include conditions as to the use of the food, as to the name by which the food shall be known, and as to the labelling, presentation and/or advertising of the food.

5.4 There are particular provisions with respect to foods which either contain or consist of a GMO. Such foodstuffs would ordinarily be subject to all the provisions of the EC Directive on the "Deliberate Release into the Environment of GMO's" (90/220/EEC), which was brought into force in the UK on 1 February 1993 by means of the Genetically Modified Organisms (Deliberate Release) Regulations 1992.

5.5 The GMO Directive expressly provides that it is *not* intended to apply to a specific area which has its own environmental assessment procedures. The Novel Foods Regulation, which of course does introduce its own procedures, runs counter to this and adds back in much of the GMO Directive compliance procedures: the application for authorisation under the centralised procedure outlined above, must, *in addition*, be accompanied by a copy of the written Consent and full technical dossier required under the GMO Directive. This means in effect that two layers of regulation need to be traversed.

6. *Criticism of the Regulation*

6.1 As noted above, the European approach, designed to place all food producers within Europe on an equal footing, is markedly different from that taken in the USA. In May last year the US government produced a policy statement to the effect that genetically modified food posed minimal health risks and need not be subject to special testing or labelling, save in exceptional circumstances. One of the first products consisting of a viable genetically modified organism likely to reach the market in the US is the Flavr Savr tomato developed by Calgene Inc. The tomato's ability to produce polygalacturonase, which causes softening, has been removed so that the tomato lasts longer. A similar tomato, produced by ICI Seeds, is being developed in this country. There is some concern that the European proposals will delay the process of bringing this tomato to the market because of the time lapse whilst authorisation is obtained.

6.2 One of the criteria under the Regulation which must be satisfied to establish that the novel food can safely be placed on the market is that the foods and/or ingredients "do not differ from similar foods or food ingredients that they may replace in the diet in such a way that their normal consumption would be nutritionally disadvantageous for the consumer". Non-novel foods introduced onto the market are not required to satisfy a similar criterion, and it could be argued that certain "junk-foods" which have replaced traditional foods in our diet could not satisfy such a requirement if it were imposed. Why then should novel foods be subject to stricter obligations? In addition, some foods which are "nutritionally disadvantageous" may have other advantages, such as being low calorie.

7. *UK Provisions as to Labelling of Foods containing Genetically Modified Material*

7.1 In January 1991 the Food Advisory Committee ("FAC") circulated guidelines on the labelling of foods produced using genetic modifications ("GMO Labelling Guidelines"). The stated intention behind the draft Guidelines in their existing form (consultation has been taking place) is that the use of some new technologies in the production of food may generate ethical and moral concerns for consumers because of the presence of GMOs in the final food. The FAC considered that labelling would only be a means of allaying these concerns where the presence or use of the GMOs could be considered to alter materially the nature of the food, and under these circumstances specific food labelling would be a means of informing consumers of this fact. Here the FAC appears to have been influenced by the "horizontal" suspicion of processes per se, irrespective of the safety of the end product.

7.2 In the Guidelines the FAC has recognised four categories of foods and food ingredients, which might be prepared using gene technology, some of which should carry a gene technology label and some of which should not. Where a label is required, the present proposal is for a statement "(Contains) products of gene technology" to be applied. A further proposal is that if a food ingredient is the product of gene technology then the ingredients list should also make this clear.

7.3 But the application of the label is unlikely to have much effect (if any) in allaying the fears of consumers about the safety of these products, since:

(a) it makes no distinction between the degree or type of genetic engineering which has taken place. This is analogous to placing a sticker on an orange saying "Treated with Chemicals" but giving no more information or detail than that;

(b) there is no mention of the mechanisms by which the safety of the product will be established before it ever reaches the market place. In other words the extremely vigorous clearance procedures which will have to have been followed under the Novel Food Regulation in respect of foods containing GMOs (as discussed above), will not be made clear to consumers.

7.4 If both the Novel Foods Regulation and the GMO Labelling Guidelines were implemented in their present form then the producer of a product, which might have no problem in meeting the "vertical" test of complying with the safety requirements under the Food Safety Act and the Consumer Protection Act, would nevertheless have the additional burden of complying with the following "horizontal" regulation:

- the centralised procedure under the Novel Foods Regulation;
- the Deliberate Release requirements under the GMO Directive; and
- the labelling requirements under the GMO Labelling Guidelines, together with any other conditions as to labelling imposed by the Commission under the Centralised procedure

7.5 We submit that to allow accretions of regulation to grow up in this manner, where perfectly good safeguards are already available under UK law following the vertical approach, is not desirable for the growth of biotechnology in the food industry in the UK and could potentially be a fetter on that industry's global competitiveness.

8. *Conclusion*

We hope to have demonstrated in this paper that too much emphasis on a horizontal approach to the regulation of biotechnology, can lead to results which will hamper the industry's global competitiveness. A more vertical approach, imposing proper incentives and sanctions to ensure compliance, is in our view a better way forward.

Evidence from the Department of Health

INTRODUCTION

1. In addressing the questions posed by the Select Committee, this response has been limited to those areas of policy where the Department of Health has lead responsibility or a major interest.

2. Other government departments take the lead in many of the areas associated with regulation of the UK biotechnology industry and global competitiveness. However, as a general point, the DH strongly supports the Government line of avoiding dual regulation ("one-stop shopping"), moving wherever appropriate away from horizontal process based regulation towards vertical product based regulation which would cover *all* aspects of assessment risk. The so called "Future Systems" approach for licensing human and veterinary medicines in the EC, which reached common position in December 1992, illustrates this commitment.

3. The DH has a specific interest in ensuring the effective application of biotechnological developments to healthcare. Within this, the DH's interest falls into several key areas: (i) human medicinal products (including those containing genetically modified organisms) for which the DH has statutory responsibility for licensing through the Medicines Control Agency, (ii) gene therapy, (iii) novel foods, (iv) in vitro diagnostic products (for laboratory and near patient testing), (v) health related research and development and (vi) intellectual property rights and patents.

To facilitate the consideration of the issues, each area will be addressed in turn.

(i) Human Medicinal Products

Q.1 *What is your interest in biotechnology?*

4. The DH through the Medicines Control Agency (MCA) has a statutory responsibility regarding the licensing of medicinal products in the UK. It reviews the safety, quality and efficacy of products defined as medicinal products under the Medicines Act (1968). It interacts with the European Commission and other member states in the licensing of medicinal products in Europe. MCA is involved in the evaluation of data for a range of products; these data are submitted by the pharmaceutical industry in support of applications for clinical trials and product licenses. Products derived from biotechnology are amongst those dealt with by the agency. To date no licenses have been issued for products *containing* GMOs, though licenses exist for products that have been *derived from* GMOs.

Q.2 *How and why is biotechnology important to UK industry?*

5. Biotechnology is likely to have a marked effect in the pharmaceutical industry, particularly in terms of product development and manufacture. The USA is dominant in the field of biopharmaceuticals. However, the biotechnology industry in the UK although relatively young is generally felt to be the most active in Europe with a high reputation for research standards (Marketletter, 20 July 1992).

Q.3 *What future prospects and opportunities does the technology offer?*

6. The number of products derived from biotechnology will increase over the next few years. Experience to date has been limited to the products *derived from* recombinant DNA technology and those utilising monoclonal antibodies, rather than those *containing* GMOs. The range of products includes human sequence insulin, human growth hormone, a number of interferons, erythropoetin and colony stimulating factors. There is scope for further development of analogues of these molecules. Monoclonal antibodies have been used to facilitate the purification of recombinant DNA products and as diagnostic tools.

7. The field of vaccine development has also benefitted from this technology. For example, yeast-derived Hepatitis B vaccine has now replaced the less safe plasma-derived alternative.

8. It has been suggested that the greatest impact of biotechnology on the pharmaceutical industries will be in the field of drug discovery. Traditional random approaches are likely to be replaced by rational drug design, made possible by for example the cloning of drug receptors.

9. The development of transgenic animals capable of expressing human genes selectively in their mammary tissues and therefore in their milk, has great potential for the production of human therapeutic products such as, for example, blood clotting factors. Research and development are moving forward quickly in the transgenics area both in the UK and USA.

Q.4 *Which developments in biotechnology raise issues of safety and how should they be addressed?*

10. The use of self-replicating vector systems for, for example, the delivery of vaccines or gene therapy products, may require that special attention is paid to the environmental impact of such therapeutics. However, in principle these will need to be assessed like any other live vaccine or product.

11. There is also a possibility that therapeutic products produced by genetic modification techniques may have different pharmacological properties than "conventionally" derived alternatives. Such concerns would be addressed by the normal licensing and approvals procedures.

Q.8 *How do current regulations compare with those of other competitor countries in Europe, In the far East and the USA?*

12. The DH through the MCA has a statutory responsibility regarding the licensing of medicinal products in the United Kingdom.

13. In the EC the placing on the market of high technology medicinal products particularly those derived from genetic modification is covered by Council Directive (87/22/EEC). The directive lays down the principles of a community mechanism for 'Concertation' such that no national decision can be made without a uniform position being reached throughout the community. This mechanism, known as the "Concertation Procedure" has helped harmonise the approach taken amongst the members states. Marketing authorizations are still granted in individual member states.

14. Experience with the "Concertation Procedure" has been positive, and it has lead, through the ongoing production of European guidelines (in which the United Kingdom has been instrumental), to a common approach to the data requirements and evaluation within Europe.

15. In December 1992, the council of Ministers reached a common position on the so-called "Future Systems" for licensing of human and veterinary medicines. Medicines containing GMOs will be subject to centralised Community procedures which will bring the pre-Licensing assessment of Medicines against the criteria of safety, quality and efficacy, together with the environmental risk assessment for GMOs (as required by 90/220) before they are placed on the market. This builds on previous work to harmonise procedures within Europe.

16. The regulatory requirements for medicinal products are similar in the USA and Japan.

Q.9 *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the United Kingdon industry, in particular as regards*

(1) *research*

(2) *product development*

(3) *investment*

(4) *location*

(5) *sales and marketing?*

17. In view of the harmonisation within Europe of the regulation of medicinal products, the United Kingdom industry should not be disadvantaged in relationship to others in Europe.

Q10. Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?

18. The UK and other European companies do not appear to have found difficulties with the procedures to date. The impact of the requirement for an environmental risk assessment for products containing GMOs and genes (Directive 90/220) is more difficult to assess though as explained above, this will be a Europe wide requirement.

Q11. How best can issues of public acceptance be addressed?

19. There is a perception that problems of public acceptance are not as acute in this field as in others. Products produced by biotechnological procedures have been in use for some years in the United Kingdom. However, issues raised by the prospect of gene therapy have been addressed by the committee on the Ethics of Gene Therapy (CEPT, the Clothier Committee)—see the following section on gene therapy.

Q12. What other factors do you consider will play a crucial role in the competitiveness of the United Kingdom biotechnology industry?

20. The main complaint of Britain's bio-industry is that there is not enough venture capital funding in the United Kingdom, leading some companies to seek funding in the USA.

(ii) GENE THERAPY

A background note on gene therapy is attached at Annex 1.

Q.3 *What future prospects and opportunities does the technology offer?*

21. Disorders in which gene factors predominate may arise from defects in single genes, or from the interaction of several genes. Such disorders affect about one per cent of children. They include cystic fibrosis, muscular dystrophy and disorders of haemoglobin. More than 3,000 single gene disorders have been described, most of which are rare. However, among them are many that are extremely disabling, and some that are inevitably fatal. Usually it is not possible to prevent or avoid most of these disorders and existing treatments can do little to alleviate them.

22. A number of single genes have been isolated and identified. This has raised the possibility that certain human disorders caused by single gene defects might be amenable to correction, and offers for the first time the prospect of effective treatment and cure.

23. Gene therapy provides an appealing future prospect for the treatment of certain types of cancer. Available chemotherapy is of the highly toxic and in many cases ineffective. Currently, there is little evidence that classical pharmacological approaches will provide a major breakthrough. In contrast, new discoveries of oncogenes and tumour suppressor genes, and the relationship of their abnormal expression to the development of human cancer, has raised hopes of new treatment using gene therapy.

24. Gene therapy is at the research stage in the UK and no licensed products exist. However the first UK proposal to apply gene therapy to a patient was approved in January 1993 by the Committee on the Ethics of

Gene Therapy, after detailed review by its expert advisors. The review was conducted in association with the MCA, the Health and Safety Executive and the Department of the Environment.

The proposal concerns a child with an inherited immune deficiency.

Q.8 *How do current regulations compare with those of other competitor countries in Europe, in the Far East and the USA?*

25. The control of gene therapy in the UK has both a statutory and non-statutory basis. The ethical issues concerned with gene therapy are currently considered by a non-statutory advisory body the Committee on the Ethics of Gene Therapy. This work will be taken forward by the Gene Therapy Advisory Committee (GTAC) which is to be set up by UK Health Ministers later this year. The safety, quality and efficacy aspects of the products used when gene modification techniques are applied to gene therapy research in patients are subject to control by the MCA (under the Medicines Act, 1968, and subsequent legislation), and the safety issues (pertaining to human health and safety and environmental safety) arising from the act of genetic modification and release of GMOs are subject to statutory control by the HSE (under the Genetically Modified Organisms (Contained Use) Regulations, 1992) and DoE (under the Genetically Modified Organisms (Deliberate Release) Regulations, 1992) respectively. There is close cooperation between the agencies, and the precise arrangements for liaison and exchange of information are under discussion by them.

26. The US Recombinant DNA Advisory Committee (RAC) provides a similar scheme for review of gene therapy research proposals as that envisaged for GTAC. This system of review also operates on a non-statutory basis. The Netherlands subjects proposals for gene therapy research to review by its national advisory committee. In France, wide-ranging draft legislation in bioethical matters, including controls on gene therapy, is under consideration. all these countries, like the UK, have to date restricted gene therapy to somatic (body) cells. They also all take the view that, in the present state of knowledge, germ line gene therapy should not be undertaken.

(iii) Novel Foods

27. The DH and the Ministry of Agriculture, Fisheries and Food have shared responsibility for this area of biotechnology policy, and they jointly support the Advisory Committee on Novel Foods and Processes (ACNFP).

Q.4 *Which developments in biotechnology raise issues of safety and how should they be addressed?*

28. The use of biotechnology to modify materials consumed as food, such as modifying farm animals to improve the nutritional properties of derived products (meat or milk) or food crop plants to introduce resistance to pests, may lead for example to the overproduction of chemicals that may be toxic, particularly in plants but possibly in animals. Such safety issues should be addressed by looking at individual food products on a case by case basis.

Q.6 *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

29. In line with UK policy in this area, vertical product legislation is favoured in the field of food biotechnology/genetic modification. The proposed EC Novel Foods Regulation, which is being negotiated for the UK by DH and MAFF is an example of vertical regulation that would cover all novel foods, not just those that are, or are derived from, genetically modified organisms. The UK line is that the Regulation should include a requirement for an assessment of impact on the environment, in keeping with Directive 90/220; those products evaluated as novel foods would then be exempt from 90/220. If negotiations are successful, when the Regulation is in place it will mean that manufacturers will have "one-stop shopping" in order to place their novel food on the market. It should also help to produce a level playing field for industry within Europe.

Q.8 *How do current regulations compare with those of other competitor countries, in Europe, in the Far East and the USA?*

30. At present, the UK has a voluntary scheme to deal with novel foods. The Food Safety Act 1990 contains powers that would enable statutory schemes to be introduced, if required; Departments are currently awaiting the results of EC discussion of the Novel Foods Regulation (see above) to inform further consideration of this area. The labelling of genetically modified foods falls within the remit of MAFF's Food Advisory Committee, which has issued proposals for comment. Food labelling generally is subject to EC control.

31. In the USA, the Food and Drug Administration announced in May 1992 that genetically modified foods would be treated like all other foods and not require special consideration or labelling. It is reported that this is responsible, at least in part, for a backlash from some consumer pressure groups to ban all genetically modified food.

Q.12 *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

32. Ethical issues play a vital role in this area. An example is the acceptability of the consumption of plants containing animal genes, and animals containing genes from different animals (including humans), to different religious and cultural sections of the population, vegans and vegetarians. An ad hoc group of the ACNFP has been set up under the chairmanship of Rev. Polkinghorne to consider these issues. There is also the wider ethical issue of whether transgenesis itself is acceptable, irrespective of whether or not these plants or animals enter the food chain.

(IV) IN VITRO DIAGNOSTICS PRODUCTS

Q.3 *What future prospects and opportunities does the technology offer?*

33. In the field of diagnosis of disease, advances in biotechnology offer the potential for the development of in vitro diagnostic products (IVDs) with improved characteristics, such as increased specificity and sensitivity. These could lead to more rapid diagnosis and also the facilitation of tests being carried out near to the patient or by the patient themselves, rather than in the traditional clinical laboratory. In addition, developments in biosensor technology may, for example, allow the continous monitoring of physiological factor in vivo.

Q.4 *Which developments in biotechnology raise issues of safety and how should they be addressed?*

34. The main aspect of safety is not related to the biotechnological aspect of the diagnostic kits, but rather to their use or rather misuse, especially where developments in technology have allowed such kits to be used outside the control of qualified personnel. Safety concerns might, for example, include misinterpretation of the result of a test and inappropriate disposal of the used kit and associated accessories.

Q.8 *How do current regulations compare with those of other competitor countries in Europe, in the Far East and the USA?*

35. There are no specific regulations covering in vitro diagnostic products sold in the UK. In some European countries certain IVDs are classed as pharmaceuticals and controlled as such. There is currently a draft EC Directive on In Vitro Diagnostic Products, and it is anticipated that this will cover products containing GMOs and will contain a requirement for an environmental risk assessment that will satisfy the requirements of 90/220. IVDs should therefore be exempt from the horizontal Directive, falling only under the vertical product Directive. It is not anticipated that this Directive will be in place before 1996.

36. In the USA, all IVDs are regulated by the Food and Drug Administration.

(V) HEALTH RELATED RESEARCH AND DEVELOPMENT

Q.1. *What is your interest in biotechnology?*

37. The DH research and development strategy has a general interest in promoting the successful development of the products of biotechnological research as part of the wealth creation process and a specific interest in ensuring the effective application of these developments within the National Health Service.

38. This means taking account of the pace of change and origin of health technologies. Not only is the pace of change rapid, but the interval between scientific discovery and practical development is becoming shorter. For example, rapid progress is being made in constructing maps of the human genome and at the same time human gene therapy is at the trial stage.

39. The application of results of research and development has informed the DH research strategy in its links with industry and its work with the DTI. This includes a number of initiatives designed to promote UK industrial innovation and competitiveness such as the DH involvement in the LINK programme, and DTI's involvement in the Biomedical Technologies research liaison committee, one of three committees established to bring together research funders to promote exchange and collaboration.

Q.12 *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

40. Future prospects for biotechnology, as for other areas of science, depend on achieving a proper understanding between those involved in the development of the science and those potential customers of this research. Ensuring that the NHS is an "informed customer" and that industry knows their needs will help to facilitate transfers of appropriate technologies. The improvement of links with industry and other research funders is an important aim of the NHS research and development strategy.

41. The development of an NHS research and development information systems strategy will provide an important avenue to alert and inform industry of research in progress that may lead to commercial possibilities, and to the simplification and standardisation of intellectual property right negotiations.

(vi) INTELLECTUAL PROPERTY RIGHTS AND PATENTS

Q.12 *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

42. Concerns have been expressed that issues of intellectual property rights and patenting rights for gene sequences and biotechnological techniques may interfere with scientific freedom and raise questions of ethics. They may also lead to increased operating costs in carrying out, for example, diagnostic tests and possible costs from litigation and compensation payments.

43. These issues may have implications for the development of techniques such as in the wider application of gene therapy and screening tests for genetic disorders.

44. A proposed Directive on the legal protection of biotechnological inventions (on which the department of Trade and Industry lead) is also currently under discussion.

Annex I: Gene Therapy

Committee on the Ethics of Gene Therapy

1. In November 1989, the Government established the Committee on the Ethics of Gene Therapy (CEGT) under the chairmanship of Sir Cecil Clothier. Amongst the Committee's terms of reference were to draw up ethical guidance for the medical profession on treatment of genetic disorders by genetic modification of human body cells and to invite and consider proposals from doctors wishing to use such therapies. The Clothier Committee reported in January 1992 (Cm 1788). Among its recommendations was that a new body should be established to oversee gene therapy research in the United Kingdom.

Government's Response

2. The Government has accepted in principle the recommendations of the Clothier Committee and has announced its intention to set up the Gene Therapy Advisory Committee (GTAC), a non-statutory advisory body, to oversee the conduct of gene therapy in the UK (Annex A). GTAC will be responsible to UK Health Ministers, who will appoint its membership.

Gene Therapy Advisory Committee

3. Although the terms of reference are to be announced, it is envisaged that the role of GTAC will be similar to that recommended by the Clothier Committee. GTAC's primary concern is expected to be whether proposed gene therapy research meets the established ethical criteria for research on human subjects. It will consider proposals for both therapeutic and non-therapeutic gene therapy research and advise on their ethical acceptability. GTAC will fulfil this responsibility by working in concert with local research ethics committees and with the bodies which already have statutory responsibilities in this field.

4. In addition, it is expected that GTAC will be charged with advising UK Health Ministers on the ethical issues arising from medical and scientific developments of gene therapy research and on any implications these developments have for public health. Ministers expect to be able to announce the terms of reference of GTAC and appoint its Chairman in Summer 1993.

Bodies with Existing Responsibilities for Gene Therapy

5. The application of gene therapy to patients is already subject to certain statutory controls which govern the quality, safety and efficacy of genetic material.

5.1 Such controls include the schemes operated by the *Medicines Control Agency (MCA)* in respect to the Medicines Act 1968 and subsequent legislation. Many gene therapy proposals will come within the scope of MCA schemes for clearance of clinical trials. For the time being, all applications of gene therapy research should be notified to MCA.

5.2 The act of genetic modification along with any activities in which genetically modified cells or organisms are cultured, stored, used, transported, destroyed or disposed of, are subject to the control of the *Health and Safety Executive (HSE)* under the Genetically Modified Organisms (Contained Use) Regulations 1992.

5.3 Gene Therapy research as a result of which particular kinds of viable genetically modified cells or organisms might spread into the environment (such as might arise from the use of viable viral vectors), requires the consent of the *Department of the Environment (DoE)* under provisions in the Genetically Modified Organisms (Deliberate Release) Regulations 1992.

6. In addition, the *General Medical Council (GMC)* and *United Kingdom Central Council for Nursing, Midwifery and Health Visiting (UKCC)* have responsibilities relating to professional and ethical conduct.

7. The existing Secretariat of the Clothier Committee has established working relationships with MCA, HSE and DoE. The precise arrangements for dealing with the exchange of information under GTAC will be discussed with those agencies in due course but close co-operation will continue.

Approval for the First UK Proposal

8. Until GTAC is in place, the Clothier Committee has agreed to remain in being to review proposals. The Committee approved the first UK proposal for gene therapy research in January 1993 after detailed review in association with the agencies described above. A copy of the Committee's press release is attached at Annex B *(not printed)*. Further proposals are under preliminary review.

Evidence from Dupont de Nemours (France) S.A. (Herve de Trogoff)

As our biotechnology operations are centred in the United States, where we have carried out numerous field studies in the past six years, I have forwarded your enquiry there and the following responses refer to the situation in the United States, not France. The focus is on the regulation of genetically engineered plants and on foods derived from new plant varieties, consistent with the major thrust of our efforts in agricultural bioechnology.

1. Our government considers biotechnology to be very important, and in December 1984 proposed a coordinated framework for its regulation, which was followed by an announcement of policy in June of 1986. Since that time agencies involved in the regulation of biotechnology products have developed their policies or regulations. For instance in June of 1987 the United States Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) published regulations on field testing of genetically engineered organisms.

Throughout the past nine years there have been numerous pronouncements coming from the Government highlighting the importance of biotechnology and the need to develop scientifically based, realistic regulatory oversight mechanisms which will not hinder the development of the technology, while promoting safety.

2. In the beginning of the debate on biotechnology environmental and food safety issues, every conceivable issue was considered, and indeed many precautions, later considered as unnecessary, were prescribed in field tests carried out in the mid and late 80's. With time it was recognized that field testing of genetically engineered plants generally did not present any greater risks than the testing of plants developed by other breeding techniques, and that the practises traditionally used by plant breeders, such as specific isolation distances between plots for different species of crop plants, would assure that the field studies could be carried out with little or no risk to the environment.

On 29th May 1992, the Food and Drug Administration published their statement of policy on foods derived from new plant varieties, wherein it specified certain potential changes in the composition of new plant varieties that may require evaluatation to assure food safety. Examples are unexpected effects, known toxicants, nutrient levels, new substances, allergenicity, etc. Most of the noted potential changes must be considered for any new plant varieties, regardless of the technique used to produce it. The potential to increase the levels of toxicants might even be greater in a wide cross than in many of the other plant breeding techniques. Just a few years ago the levels of the toxicant psoralen were increased to unacceptable levels when celery was cross-bred with a wild relative. Plant breeders have made monitoring for levels of specific toxicants in certain crop plants an integral part of breeding programs (e.g. oil seed rape, potato, celery). It is important to recognize that many the safety issues raised are not unique to genetic engineering.

The approach of the FDA in the United States is very consistent with the scientific approach outlined in the recently finalized publication of the Organisation for Economic Cooperation and Development "Safety

Evaluation of Foods Derived by Modern Biotechnology: Concepts and Principles", which was de-restricted in December, 1992. The OECD report focuses on the rigor of the scientific evaluation of a specific biotechnology food necessary to establish that the food is indeed substantially equivalent to the parent from which it was derived.

3. In the United States, biotechnology organisms and products are generally regulated by the agency which would regulate similar products which are not genetically engineered. Thus for instance all microbial pesticides are regulated by the Environmental Protection Agency, and most foods are regulated by the Food and Drug Administration, irrespective of the process used to produce them (the USDA regulates certain foods such as meat products.) There is no specific regulatory regime which covers all biotechnology products.

4. Most of the regulations pertain to general release, not to contained use.

5. Products of biotechnology are generally regulated based on the characteristics of the product, not on the process by which they are derived. The process is one of the triggers for regulation by APHIS, but APHIS evaluates the products according to their characteristics. In the past six years, APHIS has approved over 350 field studies of genetically engineered organisms, the overwhelming majority being plants. Based on the information derived from these field tests, APHIS, on 31 March 1993, published a regulation allowing for field testing of six species of genetically engineered crops, namely cotton, corn, soybeans, tomato, potato and tobacco, within 30 days after notification of APHIS. In the past no genetically engineered plants could be field tested without a permit, which took roughly 120 days to obtain.

In the same 31 March 1993, publication, APHIS outlined the procedure, and the data necessary, for exempting products from their regulatory oversight.

The second half of the regulatory equation for genetically engineered plants is food safety. The Food and Drug Administration is regulating foods derived from new plant varieties strictly on a "vertical" or product-based basis (see point 2 above). The FDA acknowledges in its policy statement that new plant varieties prepared by any technique may raise certain safety issues and that recombinant DNA techniques, since they are more precise, "increase the potential for safe, better-characterized and more predictable foods".

Thus it is clear that "vertical" regulation is preferred by the Government.

In all of the discussions of safety issues surrounding the field testing of new experimental crop varieties, and the safety of foods derived from such crops, recognition must be given to the remarkable safety record in traditional plant breeding.

In FDA's discussion of potential changes in composition that may require evaluation to assure food safety, it is recognized that well-established practices of plant breeders have successfully identified and eliminated plants that exhibit unexpected, adverse traits or plants with unacceptably high levels of toxicants, prior to commercialization.

6. The regulatory oversight mechanisms in the United States have allowed companies to readily field test genetically engineered crops and thus have clearly promoted the technology versus certain countries where there may be many bureaucratic, process-based constraints. The regulatory system has contributed to the development of a large data base on field testing and a recognition by both the regulated community and the regulators that there is a need for the elimination of redundant and unnecessary paper work, and a streamlining of the regulatory schemes such that scarce resources can be directed to those products truly meriting them. The new APHIS notification procedure for the six crops noted above, the APHIS procedure for deregulation of Specific products, and the FDA policy statement on foods derived from new plant varieties should stimulate research and product development, and contribute to an ever-expanding knowledge base. This should help improve the climate for investment and increase the chances of products reaching the marketing stage.

Question six asks for the consequences of the regulatory regime on the competitiveness of our firm in regards to certain elements important to the eventual commercial success of biotechnology.A very important consideration is the consequences of regulatory regimes on the competitiveness of the technology itself vis-a-vis competing technologies.

Overly-restrictive governmental policies could lead companies to eschew a technology which the FDA fells "Increases the potential for safe, better-characterized and more predictable foods" and strictly focus on the older, albeit perhaps more time-consuming technologies.

7. Since biotechnology is so broad and since to date there are no commercial genetically engineered crops. it is hard to give any definitive answer to this question. There has, however,been very little opposition to the more than 350 field tests carried out in the past six years, and no examples, to my knowledge, of destruction of field test plots. In the past year there have been a considerable number of newspaper articles on foods from genetically engineered crops, some favorable, some not, with the latter often colored by a focus on examples of exotic types of foods that could conceivably be produced by genetically engineering while neglecting the more mundane type of products that will likely represent the vast majority of the true candidates for commercialisation.

Given the opportunity to blossom, we believe that the many future products of agricultural biotechnology, such as healthier, more stable cooking oils, more nutrituous proteins, better tasting fresh fruits and vegetables that may be less susceptible to spoilage, just to name a few, will be accepted by the consumer in the United States

Evidence from John Durant, Assistent Director, Science Museum

I write in my capacity as Chairman of the European Federation of Biotechnology Task Group on Public Perceptions of Biotechnlogy, in order to contribute evidence to your sub-committee, chaired by Lord Howie of Troon, on "Regulation of the UK Biotechnology Industry and Global Competitiveness". I enclose a brief description of the terms of reference and current activities of this Task Group, which I trust will serve to explain the nature of my own and my Task Group's interest in biotechnology.

I note that the terms of reference of Lord Howie's sub-committee include matters to do not only with the development and regulation of biotechnology in the United Kingdom, but also with issues of public acceptance (listed item 11). It is on this latter subject, in particular, that I and my Task Group wish to comment. we do so in the knowledge that the issue of public acceptance is of growing concern to scientists, industrialists and policy-makers working in the field of biotechnology. we are convinced that an appropriate response to this issue is essential to the future development and exploitation of biotechnology.

The following are the key points that we should like to draw to your sub-committee's attention:

1. Evidence from a recent European Commission survey (Eurobarometer 35.1, 1991), as well as independent research by other groups, confirms that there is a very low level of public awareness of biotechnology as such, together with low levels of awareness and understanding in relation to many specific areas of biotechnological research. For example, a recent study of public perceptions and media coverage of the Human Genome Project (HGP) in Britain, which was conducted for the European Commission by me and my colleagues Dr. Martin Bauer and Dr. Anders Hansen, found no awareness whatever of the HGP among randomly chosen representatives of the general public, This was linked to minimal coverage of the HGP in the popular press during the period covered by the study.

Recommendation 1: Science, industry and government should collaborate to raise levels of public awareness and understanding of biotechnology.

2. Evidence from the same sources indicates that the European public possesses whay may be termed ambivalent attitudes towards biotechnology. While some biotechnologies are regarded as socially beneficial, others are regarded as potentially dangerous and/or unethical. In general, medical biotechnologies aimed at the prevention or cure of serious genetic illnesses are regarded more favourably, whereas agricultural and industrial biotechnologies aimed at what appear to the general public to be less obviously important goals, are regarded less favourably.

While the British public is generally supportive of medical biotechnologies, concern is expressed about the possible abuse of such technologies for "eugenic"purposes. Also, problems are perceived in connection with personal identification and personal privacy. DNA fingerprinting, in particular, is widely regarded as a successful and useful technology in the field of forensic science; but it is seen as a potential cause of difficulty in the field of personal insurance.

In general, non-medical biotechnologies that appear to promise major practical benefits (such as the development of new crop varieties for use in developing countries) are welcomed by the British public, in spite of perceived disbenefits or risks; whereas those that appear to promise minor practical benefits (such as the development of new crop varieties with better handling qualities, for use in developed countries) are regarded less favourably, even where no clear disbenefits or risks are apparent. Genetic manipulation of farm animals would appear to be one of the least popular biotechnologies in the UK.

Recommendation 2: Substantive social benefits deriving from approved biotechnological applications, together with any regulatory restrictions that govern dangerous and/or frivolous biotechnological applications, should be strongly emphasised in public communications.

3. This pattern of low levels of public awareness and understanding, on the one hand, and ambivalent attitudes, on the other, is cause for concern. It is vital that the scientific and industrial communities in Britain and the rest of Europe should work to increase public awareness and understanding of biotechnology. At the same time, we would suggest that a large body of research on public attitudes to science and technology suggests that public awareness and understanding of the relevant scientific principles and processes are not as crucial to the formation of attitudes as public confidence and trust in the relevant scientific and industrial institutions.

A case in point is the finding in the recent Eurobarometer survey that while both the Danish and the German publics regard biotechnology as inherently risky, the Danish public is generally more favourably disposed towards the continued development of biotechnology than the German public. This may be because the Danish public is more confident in the governmental, scientific and industrial institutions of biotechnology (see Durant Ed., 1992, pp. 52-108). We note that Denmark has pioneered over many years the development of open and constructive dialogue between the scientific and industrial communities and the general public.

Recommendation 3: The maintenance of public confidence and trust in the institutions of biotechnology should be regarded as a primary aim of regulatory policy. Consideration should be given to new ways of fostering constructive dialogue between the biotechnological community and the general public, such as Danish-style "consensus conferences".

Finally, I should like to apologise for the slightly late date of this submission. I hope very much that it may be accepted, and that the points we have made may be useful to your sub-committee. If your colleagues should require further clarification of any points made in this submission, we shall be happy to oblige.

* *References:*

The Human Genome Project and the British Public, J Durant, A Hansen, M Bauer, A Gosling, February 1993. A final report to the European Commission of a research project "Public Awareness and Media Coverage of the Human Genome Project in Britain".

Biotechnology in Public. A Review of Recent Research. (J Durant Ed, with an introduction), Science Museum, London, 1992.

Letter to The Clerk from Gerard Fairtlough

In your letter of 19th February, you invited me to submit written evidence to the House of Lords Sub-Committee enquiring into "Regulation of the UK Biotechnology Industry and Global Competitiveness". My submission is given below.

EXECUTIVE SUMMARY

The UK is strong in basic biological science and globally competitive in most of the industrial sectors likely to be affected by biotechnology during the next two decades. Since the UK has desperate need of greater industrial competitiveness, it would seem essential to give every reasonable support to the strong industrial sectors. The right regulatory position is a key element in such support.

There is strong evidence that biotechnology *per se* does not carry any special risks. Therefore vertical regulation is generally to be preferred. However, as a general safeguard, some continued control of genetic manipulation could be justified.

UK national regulation is generally strong but sensible. This is an important advantage for UK-based firms and should be sustained. There is a danger that EC regulation may be different from and less flexible than the UK's, which might become a serious problem for industry. A good record of safety, plus open debate of the issues, is the best way to gain public acceptance for biotechnology.

Apart from regulation, other factors affecting industrial competitiveness are: the education and training which a country provides for its people, the science base, the system for public procurement, the financial system and the system for corporate control. Getting the last of these right is vital, so as to avoid short-termism.

MY INTEREST IN BIOTECHNOLOGY

In this evidence I assume that "biotechnology" refers to advanced biotechnology, which make use of techniques such as recombinant-DNA manipulation and monoclonal antibody production, which were discovered in the mid-1970s. My interest in the field started in the late-1970's, when I was a Divisional Director at the National Enterprise Board. While at the NEB, I led the team which founded Celltech Limited (now Celltech Group plc) the UK's first advanced biotechnology company. On its formation, I became Celltech's Chief Executive and held that post until my retirement in 1990.

Since then I have been a non-executive director of two biotechnology companies—Cantab Pharmaceuticals plc and Therexsys Limited. I am a council member of the Science and Engineering Research Council and of the Sainsbury Laboratory for Molecular Plant Pathology, part of the John Innes Centre at Norwich.

I am also a specialist adviser to the House of Commons Select Committee for Science and Technology. I have interests in technology policy and technology managment and links to the Science Policy Research Unit at Sussex University and the Centre for Technology Strategy at the Open University.

THE IMPORTANCE AND FUTURE PROSPECTS OF BIOTECHNOLOGY

(1) *Human Health*

The rapid expansion in biological knowledge which has taken place during the past twenty years is largely based on the techniques of biotechnology. This has, in turn, led to many important new therapies, to valuable diagnostic tools and to the transformation of pharmaceutical research, with a much more rational approach then before. The potential for further advances is in no way exhausted. Research into the human genome, protein structure-function relationships, gene regulation, developmental biology, neurobiology and into many other areas will transform the treatment of inherited disorders (like cystic fibrosis), of cancer, of viral diseases (like AIDS), of cardiovascular disease and, in due course, of neurological disorders. Improved disgnostic methods will help to forecast individual susceptibility to many diseases and to choose the best individual treatments.

Pharmaceuticals is one of the few industries in which the UK is clearly a world leader. Since biotechnology will be the basis for nearly all future drug discovery, and often for drug use, its industrial importance to the UK is, on this score alone, very considerable.

(2) *Agriculture, Food and Drink*

Advances in understanding of the biology of crop plants and the ability to improve these plants through biotechnology, will have major effects on world agriculture within the coming decade. These will, in turn, influence industries supplying agriculture, such as the seeds business, and industries supplied by agriculture, such as food and drink. These industries will also be directly influenced by biotechnology, as a research tool, through gene manipulation and through new bioprocesses. Animal health and animal breeding are benefiting from the advances in human health and biological science.

The UK is globally competitive in a number of areas within agriculture itself and in industries supplying and supplied by agriculture.

(3) *Chemical Process Industries*

Bioprocesses are spreading steadily within the chemical process industries and may become seriously important to them within the next decade. The UK has considerable strength in these industries.

(4) *Conclusion*

The UK is strong on basic biological science and is either highly competitive or reasonably competitive globally in most of the industrial sectors likely to be affected by biotechnology during the next two decades. This is a vital opportunity. Since the UK has desperate need of greater industrial competitiveness, it would, in my opinion, be very unwise not to give every reasonable support to the bio-industries. The right regulatory position is a key element in such support.

SAFETY ISSUES AND MODES OF REGULATION

(5) *Research and Manufacturing Processes*

There is now 20 years of experience in the use of biotechnology in research and in the manufacture of a variety of products. This experience has given no cause whatever for alarm. Initially regulation was very strict and it is still careful. Evolution from a horizontal to a vertical approach has, to some extent, taken place. In my opinion, the horizontal aspects which remain are probably desirable, since they are administered reasonably. The reasons why some control of genetic manipulation should remain are, first, that in the event of any problem (in my view, extraordinarily unlikely), it would be easier to correct it and, second, that the continuation of this control is reassuring to the general public.

(6) *Human Health*

Vertical regulation is extensively developed, both in the regulation of drugs and in ethical judgments on clinical practice, and should continue. Radically new products and procedures should continue to be introduced very carefully, especially for non life-threatening diseases, and then given reduced regulation as their safety is proved in practice.

(7) *Animal Health and Husbandry*

Most scientists feel that the objections which have been raised against animal husbandry products made by recombinant-DNA techniques, such as bovine growth hormone, are particularly far-fetched. I think the reasons for this is that the objectors confused "horizontal" issues ie, the way in which the products were made, with "vertical" issues, like animal welfare and farm economics. The confusion was no doubt deliberate on the part of some objectors. This example seems to me to argue for a move to vertical regulation, in every field, as soon as reasonably possible.

(8) *Deliberate Release*

The deliberate release of genetically-modified microorganisms clearly raises weighty issues. Experience is, so far, very limited and if problems did arise it would be hard to control them. This would argue for a continuation of special regulation of the deliberate release of genetically modified microorganisms.

This is another area in which "vertical" and "horizontal" issues have not been clearly separated. Although I have suggested that issues related to genetic manipulation might need special regulation, it is far from clear that there are, in fact, any real problems on this score. However, the history of the deliberate release of new organisms (not genetically manipulated) into established ecosystems, like the release of rabbits in Australia, has not been one of unqualified success. Well-judged regulation would seem to require a clear separation between the issue of genetic manipulation and that of ecosystemic effect.

(9) *Military and Terrorist Use of Biotechnology*

Although I am no expert in these fields, it does seem likely that biotechnology could provide new scope for biological warfare or terrorist threats. It is doubtful whether regulation will be able seriously to reduce these risks, but I suppose that continued supervision of genetic manipulation might have some slight advantage on these grounds.

(10) *Conclusion*

There is strong evidence that biotechnology *per se* does not carry any special risks. Therefore vertical regulation is generally to be preferred. However, as a general safeguard, some continued control of genetic manipulation could be justified.

COMPARISON WITH OTHER COUNTRIES AND IMPACT ON INDUSTRY AND THE SCIENCE BASE

(11) *UK National Regulations*

To the best of my knowledge, the current UK national regulations affecting biotechnology are either equally or more favourable to industry than those of any competitor country, in Europe, the Far East or North America. In the case of regulation affecting genetic manipulation, UK national regulation is broadly similar to that in the USA and in European countries such as France and Holland. UK and EC regulation of drugs is somewhat more flexible than that of the US Food and Drug Administration, but on balance equally stringent.

(12) *EC Regulations*

The chief area for concern is the interaction between UK and EC regulation. If industry is obliged to comply with two quite different sets of regulations, the costs of compliance can increase many-fold and the extra uncertainty can be damaging to product innovation. Furthermore, at least in the area of the deliberate release of genetically modified microorganisms, the EC regulations seem likely to be more legalistic and more subject to unpredictable pressures, than the UK's. The hostility in Germany to "genetic engineering", possibly as a reaction to what was done by the Nazis, has been reflected in very restrictive action by the governments of some Länder. If these attitudes were to influence EC regulations, the result could be a serious problem for UK industry.

(13) *Impact on Industry and the Science Base*

The UK has a long history of careful and well-judged regulation in most fields, including pharmaceuticals, agrochemicals, and, in a non-product area, health and safety at work. The UK's regulation has avoided excessively legalistic or bureaucratic methods, but has been stringent enough to command respect throughout the world. It has also been based, for the most part, on careful analysis of new situations. I believe regulation of this kind is exactly what industry needs and it is no accident that, in regulated fields, international firms have found the UK to be an excellent place to carry out research and to manufacture. This advantage should be sustained.

(14) *Conclusion*

UK national regulation is strong but sensible. This is an important advantage for UK-based firms and for UK science and should be sustained. There is a danger that EC regulation may be different from and less flexible than the UK's, which might become a serious problem for industry.

PUBLIC ACCEPTANCE

(15) *A Good Record*

The best long-term guarantee of public acceptance of biotechnology is a superb safety record, achieved by successful regulation and good practice in industry and science. A high reputation of this kind is likely to be earned by stringent regulation of any completely new technology, followed by relaxation as a record of safety and sound practice is established.

(16) *Public Debate*

Contributory factors leading to public acceptance, will be thorough analysis of any potential problems, with open discussion of the results of that analysis, and the avoidance of political gestures in reaction to public pressure. I do not think that public relations campaigns on the regulation of biotechnology will usually be helpful, although engaging public interest in open and informed debate on specific issues is important.

(17) *Economic Research*

Research into the economics of regulation (generally and specifically for biotechnology) should be encouraged, probably by the Economic and Social Research Council. It would be useful to have case studies on the costs to industry and the public of different regulatory approaches. For example, a comparison could be made between the costs of continuing well-judged regulation with those of regulation which is initially lax but which later becomes much tougher in response to public pressure.

(18) *Conclusion*

A good record of safety, plus open debate of the issues, is the best way to gain public acceptance.

OTHER FACTORS AFFECTING INDUSTRIAL COMPETITIVENESS

(19) Of course, the right regulatory system is only one of the factors affecting industrial competitiveness. I consider that the most important of the other factors are the education and training which a country provides for its people, the science base, the system for public procurement, the financial system and the system for corporate control. Getting the last of these right is vital, so as to avoid short-termism.

I hope my evidence will be of use to the Sub-Committee.

Evidence from the Farm Animal Welfare Council (FAWC)

A. SUMMARY

FAWC's comments are heavily biased towards farm animals and the protection of these animals' welfare. There may be adverse effects on welfare which would not have occurred if the new technology had not been used, for example the consequences of painful deformities. Conversely, it may be that welfare will be improved as a consequence of the new procedure, for example if disease resistance is increased.

B. COMMENTS ON THE QUESTIONS POSED BY THE SUB-COMMITTEE

1. FAWC is interested in biotechnology from the viewpoint of the welfare of animals which have been produced from modifications of their basic genetic make-up by modern techniques of gene manipulation.

2/3. Developments in biotechnology can lead to improved disease control and also more efficient production of food but without proper controls there can also be welfare problems. The use of biotechnology to impart genetic resistance to infectious and metabolic diseases in farm animals is a positive move. However, the manipulation of animals to produce more meat and milk has the potential to create problems. These include the manipulation of body size or reproductive capacity by breeding, nutrition, hormone therapy or gene insertion in such a way as to reduce mobility, increase the risk of injury, metabolic disease, skeletal or obstetric problems, perinatal mortality or psychological distress.

Another area which has additional ethical implications is the insertion of human genes into farm animals so that they can serve man as sources of (i) pharmaceuticals, (ii) cells, tissues and organs.

4. By genetic manipulation, peculiar and unnatural animals may result which have characteristics which are undesirable and whose welfare may be compromised. Presently, research on animals is controlled by the Animals (Scientific Procedures) Act 1986 which requires researchers to demonstrate to the Home Office the integrity of the work and that there will be benefits from it.

Transgenic animals and animals treated with biotechnical products should have their welfare assessed using proper scientific measures. It may be necessary to monitor over at least two generations before being allowed into general commercial use.

5. The industry must be regulated and at the research stage the Animals (Scientific Procedures) Act 1986 must apply. There may, however, be a gap in control between initial scientific development and commercial use. This area needs to be considered. Once a genetically manipulated farm animal is available commercially its welfare is protected by existing welfare legislation, codes of practice and by recommendations made by FAWC; but there is no requirement to notify a regulatory body once the technique moves from the development stage, so how can it be monitored? There is a view that the commercial application of biotechnology in farm animals should be subject to a law similar to the 1986 Act.

6. The horizontal approach is required and later, at the appropriate stage, the vertical approach. From an animal welfare viewpoint, it is essential that a new process should be judged not on results but on the process itself.

7. There needs to be examination of the effects on animal welfare and, initially, regulation should be based on the process.

8. FAWC does not have detailed knowledge of controls elsewhere but believes that in terms of animal welfare, the UK is more advanced than most.

9. Research is already controlled by the Animals (Scientific Procedures) Act, so there should not be a major effect. Product development is protected under licence but additional regulation may lead to additional costs.

10. There is a risk that regulation may restrict implementation but some form of control is essential. A balance is essential and legislation and/or codes of practice must be reasonable.

11. A programme of education is required. This is an emotive topic and the public need the facts. Public acceptance is enormously important and unless the procedures are acceptable, it will be very difficult for them to succeed.

12. The research has to be well-funded and worthwhile. Government and industry both have a part to play.

Farm Animal Welfare Council

March 1993

Evidence from the Food & Drink Federation

1. *The interest of the food industry in biotechnology*

Biotechnology in the broad sense has formed the basis of much of food processing since antiquity; in the present context we are referring to the recent extension of biotechnology in the genetic modifaction of crop plants and food microorganisms by molecular biological techniques.

By facilitating precision breeding of crops and food grade microbes and specifically introducing defined improved traits we anticipate benefits in agriculture, manufacture and comsumer appeal; reduction in the need for pesticides in agriculture and distribution; reduced fertiliser needs; more efficient use of enzymes in processing; better product shelf life in distibution and the home; better fresh and processed product flavour and texture etc. Thus all sectors of the food chain can benefit from the technology.

2. *How and why is biotechnology important to UK industry*

Agricultural competitiveness and food cost and quality will be enhanced by the use of genetically modified crop and microorganisms, as exemplified below. It is important that the UK industry is not disadvantaged by measures which prevent the use of safe products available to our competitors, and that the consumer is not prevented from benefitting from such products.

3. *What future prospects and opportunities does the technology offer?*

Molecular genetic techniques provide faster, more accurate development of new varieties than conventional breeding, and are less likely to have unintended side effects. They also provide the possibility of generating varieties that would be very difficult to obtain by conventional breeding.

A selection of the existing and potential transgenic plants and microbes shows the types of benefits that may be obtained in the food chain;

Modification	*Effect*	*Benefit*
Enzyme in fruit cell walls	Slower softening in ripening	Fuller, riper flavours longer shelf life, higher solids.
Insertion of insect antifeedants, viral coat proteins	Insect resistance, virus resistance	Reduction in pesticide use lower cost in agriculture.
Transgenic enzymes	Fermentation production of plant and animal enzymes	Lower manufacturing cost avoidance of animal products.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

Food Safety Issues

Gentic Modification *per se* present no special food safety risk: modified genes, like the rest of the DNA present in food, are digested and cannot be incorporated into our own genetic makeup. So, provided the characteristics for which the inserted genes code, if they are present in the food, are themselves safe, the modified organism will be as safe as the unmodified.

We concur with the views of the OECD[1] and the US FDA[2] that foods produced with GMOs do not represent a special class of new foods and that they should be subject to the same type of risk assessment as any other new food product, ie an assessment that is based on the objective qualities of the food product and its intended use, rather than its method of development, Thus, new varieties of plants, livestock or microbes, whether produced by conventional breeding or using recombinant DNA techniques, should be subject to a risk assessment, by the producer, which considers the potential for introducing adverse toxicological or nutritional changes to the food.

The OECD Report[1], 1992 "Concepts and Principles Underpinning Safety Evaluation of Foods Derived by Modern Biotechnology" advises that:

> *Modern biotechnology broadens the scope of the genetic changes that can be made in food organisms and broadens the scope of posible sources of foods. This does not inherently lead to food that is less safe than food(s) developed by conventional techniques. Therefore the evaluation of food and food components obtained from organisms developed by the applicaton of the newer techniques does not necessitate a fundamental change in establised principles, not does it require a different standard of safety.*
>
> For foods and food components from organisms developed by the application of modern biotechnology, the most practicable approach to the determination of safety is to consider whether they are *substantially equivalent* to analogous conventional food product(s), if such exist. ...

Application of the principles of substantial equivalence and selection of safety data requirements on the basis of risk assessment will assure safety without putting unjustified demands on innovators or on expert review bodies.

Environmental issues

There have been cases of environmental damage arising from the introduction of a new species, such as the European rabbit in Australia, into an environment in which the species is not naturally contained. Similar risks potentially exist from the introduction of a new gene giving a new advantage, such as pest resistance, into a population, from which it may spread by natural breeding. FDF agrees that environmental risk assessments are therefore, quite correctly, required by existing UK legislation[4]. They are also required by a European Directive[5] which will shortly be implemented in the UK.

5. *Should biotechnology be regulated by an industry specific regime?*

6. *Should regulation be horizontal (defined by the process by which a product is derived) or vertical (defined by the product's characteristics)?*

For the reasons given above, in answer to question 4, we believe that the existing regulatory framework, based on product characteristics, is appropriate for the assurance of food safety. Whilst additives to foods are regulated, there is neither UK nor European regulation governing the introduction of new foods. In the UK there is a voluntary system of review by the Advisory Committee on Novel Foods and Processes (ACNFP).

The FDF supports the need for European legislation covering the introduction of novel foods. FDF considers that *special* legislation on the safety of foods produced by genetically modified organisms is unnecessary. FDF supports a common, risk based approach to review of all novel foods, including those derived from or comprising GMOs. Such an approach has been put forward by the ACNFP[3] in the UK and the FDA in the USA as well as the OECD Group of National Experts on Safety in Biotechnology.

The recent approach of the CEC in its draft Novel Foods regulation focuses on the technology used in generating a new food, highlighting foods produced from GMOs for special regulation. We believe that this is unnecessary for consumer protection, could seriously disadvantage the competitive position of Europe's agriculture and food industries, and will become quickly obsolete.

Regulations about technology are liable to be overtaken by technology. We are seeing this already with genetic modification. Initially most genetic modification involved cutting out a piece of the DNA containing the required gene from one organism and putting it into a DNA chain in the plant or animal or microbe that was to be altered. Now, it is increasingly possible to make genes for particular purposes, by copying a gene found in an existing gene pool and adapting it to work in a different plant, for example, or by designing from scratch to give the control instructions or make the protein that is needed. It is also possible, by knowing the sequence of a desirable gene, to search for it in the natural population and so select it for conventional breeding.

Since molecular genetics pervade modern breeding methods, certain simplistic concepts cease to be either precise or pertinent. Such concepts, including the terms "gene technology" and "genetic modification" have sometimes been given legal status.

7. *Should regulation evolve from a horizontal to vertical approach?*

As we have indicated above, we see no need for a horizontal approach in food safety legislation.

Environmental legislation, however, must be horizontal in the sense that a common approach to risk assessment and clearance should be made, irrespective of the end product or application. Risk assessments are required by existing UK legislation[4]. They are also required by a European Directive[5] which will shortly be implemented in the UK.

Although we do not see GMOs is generically different from new varieties generated by conventional methods, we recognise that at the present early stage in the development of a technology a cautious approach is prudent, and that independent expert review is desirable for certain classes of risk. However, we believe that as understanding of the potential hazards increases it will become possible to exempt many types of modification from the notification and consent requirements.

8. *How do current regulations compare with those of other competitor countries?*

In Europe a common regulation for novel foods is being debated in Council and Parliament. In most member states genetically modified organisms in foods are not specifically regulated.

We are not familar with the regulations in the Far East.

The approach of the US Food and Drugs Administration has been to treat genetically modified organisms in the same way as other new food items, and not to develop specific legislation.

Worldwide, regulations or biotechnology are in an early stage of development. Unnecessarily restrictive regulations should be avoided as this could damage the competiveness of UK industries. Restrictive regulations in Germany, for example, have led to the transfer of many research efforts to other countries.

9. *What are the consequences of the regulatory regime on the competitiveness of the UK food industry?*

At present, uncertainty over the likely outcome of the debates on regulations acts as a deterrent to food manufacturers adopting the use of genetically modified organisms in the UK and elsewhere in Europe. Research and development is progressing further and faster in the USA, with a number of crops in lage scale field trials.

If the UK or Europe were to adopt more restrictive legislation, or to seriously delay regulation, the UK agriculture and food industries would be disadvantaged competitively. Regulatory difference could also present anticompetitive barriers to trade and may have implications for GATT agreements.

10. *Is there a danger that the present regime will prevent the exploitation by British industry of research conducted in the UK science base?*

The doubts alluded to in our answer to the previous question restrict the commitment to research and exploitation.

The UK science base is particularly strong in certain areas, such as protein engineering, and molecular biology in the context of food microbiology. Exploitation of the latter is not seriously impeded and contributes to improving the safety of food. The former has a greater potential economic benefit, which is unlikely to be fully realised in the present climate.

11. *How best can issues of acceptance be addressed?*

Public confidence is an essential prerequisite for investment in development and marketing of food products of genetically modified organisms to proceed.

FDF believes that consumer education is urgently required to increase public understanding of the nature and benefits of genetic manipulation in its various applications to food production. It is up to the food industry to convey the benefits of any new product or technology; however, the regulatory environment has an important part to play in consumer perception.

Labelling issues: We agree with the FAC in that "we firmly believe that labelling should not be used as a substitute for education". The public should be aware that there are requirements for the safety evaluation of any kind of "novel" food and FDF does not believe that labelling is an essential adjunct to confidence in fulfilment of those requirements.

There is a real danger that any kind of special labelling in respect of GMO use will only serve to reinforce popular misconceptions about food technologies rather than provide factual information to help the consumer better to understand the processes used to produce a food or drink.

Ethical issues: The debate on genetic modification, in some quarters, goes beyond the pragmatic issues of environmental and consumer safety, assuming an ethical dimension, the main theme of which is that Man should not tamper with Nature. This belief is, in part, born of lack of confidence in the scientists' ability to predict the results of gene technology, coupled with the supposition that genetic modification by recombinant DNA methods is fundamentally different from "natural" development of the gene pool and from Man's conventional breeding.

In fact mutation and DNA recombination is commonplace in Nature, and the effects of the reassortment of genes that occurs in natural breeding and in breeding programmes are less predictable and less specific than those of controlled genetic modification using recombinant DNA. In our view the new techniques are not so fundamentally different from more conventional breeding that they pose qualitatively new risks. We do not see therefore, any wholly new ethical issues arising from the technology.

We welcome the Minister of Agriculture's initiative in establishing an advisory committee to address the ethical considerations involved in the application of genetic manipulation to food. We believe that the substantive issues are correctly identified in the MAFF paper[6] as those of the needs of religious minority groups and other societal taboos.

FDF argues that religious taboos are best provided for by the established method of definition by the religious authority and voluntary positive labelling of food conforming to those standards, as is presently the case with for example, kosher food.

We believe that increasing public understanding of genetic technology and its benefits will lead to increased consumer confidence and acceptance that in few cases do GMOs present ethical concerns.

12. *What other factors will play a crucial role in the competitiveness of the UK biotechnology industry?*

In the food context, there is no such thing as a biotechnology industry. Biotechnology is a pervasive part of the industry's everyday toolkit; its extension to the use of molecular genetics is a natural development.

References

1. Concepts and principles underpinning safety evaluations of food derived from modern biotechnology. OECD Group of National Experts on Safety in Biotechnology; COM/ENV/DSTI/EC/BT (91) 80/Rev 1; 1992.

2. Statement of Policy: Foods derived from new plant varieties. Food and Drug Administration of the US Department of Health and Human Services; Notice, Federal Register 57, no. 104, 29 May 1992.

3. Guidelines on the Assessment of Novel Foods and Processes; Department of Health, Advisory Committee on Novel Foods and Processes, London, 1991.

4. The Genetic Manipulation Regulations 1989, SI 1989 No 1810.

5. Directive 90/220/EEC on the deliberate release to the environment of genetically modified organisms.

6. MAFF consultation paper: Genetic Modification Programmes and Food Use. 25 September 1992.

Translation of evidence received from the French Ministry of Agriculture and Fisheries (formerly the Ministry of Agriculture and Rural Development)

1. *How important does your Government perceive biotechnology to be?*

The Committee of Enquiry on Release of the Products of Biotechonology was set up in 1986 by decree of the Ministry of Agriculture.

The Act of 13 July 1992 sets a framework for implementing EEC Directives 90/219 and 90/220 of 23 April 1990.

This Act re-establishes the Committee on Genetic Engineering with the remit of assessing the risks presented by GMOs, and the procedures used for deriving them; and the Committee of Enquiry on Release of the Products of Biotechnology with the remit of assessing the risks associated with deliberate release of GMOs.

2. *Which developments in biotechnology are thought to raise safety issues?*

The two chief scientific problems which will be faced by the Advisory Committee on Release of the Products of Biotechnology are:

- resistance of plants to total herbicides;
- resistance of plants to viruses.

Each file deposited before this Committee assesses the potential risk of the proposed experiment.

3. *In your country, is biotechnology regulated by a specific regulatory regime?*

The Act of 13 July 1992 may be considered as a regulatory regime peculiar to biotechnology. Indeed, this Act envisages that:

- each use of GMOs for the purposes of research or teaching is subject to specific consent;
- each deliberate release into the environment for the purposes of R&D is subject to specific consent.

4. *Do regulations distinguish between contained use and general release (for experiment or marketing)?*

The regulations make a distinction between contained use and deliberate release.

5. *Is regulation in your country "horizontal" (where a product is judged through the process by which it is derived) or "vertical" (where a product is judged by its characteristics)? Which is preferred by your Government?*

The regulations have a vertical approach. A product is judged on its characteristics. For GMOs, assessment is on a sectoral basis and the advice of the Committee of Enquiry on Release of Products of Biotechnology is required. This is the Government's choice.

6. *Is biotechnology publicly accepted in your country?*

There is no specific study of public acceptability of biotechnology in France, but no negative reaction has been recorded.

7. *Has your Government implemented EC Comission Directives 90/219/EEC and 90/220/EEC. If so, how? If not, when do you expect to do so?*

EEC Directives 90/219 and 90/220 have been partially transposed into domestic law by the Act of 13 July 1992. The implementation decrees are in the process of preparation.:

Ministerial responsibilities are as follows:

Contained Use:

Research: Ministry of Research.

Industry: Ministry of the Environment.

Deliberate Release:

Research and Development: when the product is tested for putting on the market, the competent ministry with competence in that sector.

When it concerns basic research, the competent ministry is the ministry of research.

When there is no sectoral procedure for consent, the competent ministry is the ministry of the environment.

Supplementary evidence from Glaxo Group Research Limited (Microbiology Division)

Comparison of USA NIH Guidelines on Genetically Manipulated Organisms (GMOs) with UK Regulations

The following summary is based on discussions with the Biological Safety Officer at Glaxo Research Institute, North Carolina and on the published National Institutes of Health Guidelines for Research involving DNA molecules (Federal Register Vol 51 no 88 and Vol 56 no 138). These guidelines are voluntarily adhered to by Glaxo Research Institute and by other US companies; there is no special statutory legislation for GMOs in the United States.

The NIH guidelines require the establishment of an Institutional Biosafety Committee (IBC) whose overall role is similar to the Genetic Modification Safety Committee in UK institutions. The main difference is the stringency of the regulations these bodies are required to apply to a given problem and subsequently the time delays and increased workload experienced in the UK relative to the USA for the same situation.

According to the NIH guidelines, work with a "typical" GMO (ie one expressing a non-toxic gene product in a disabled host bearing a poorly mobilisable plasmid) below the 10 litre scale of fermentation requires no notification of the IBC. ("Toxic" in this context is considered to be an LD50 in vertebrates of below 100 microgrammes per kilogram body weight). For work above the 10 litre scale with such a GMO, no prior notification of the IBC is necessary, but a registration document describing the source and nature of the DNA, host and protein must be lodged with the IBC. Scale-up is carried out to GLSP; higher levels of containment are not needed unless, for example, the GMO is a pathogen or expresses a toxic gene product.

In contrast, UK regulations require local written consent for all GMO work and notification to the government Health and Safety Executive. Organisms classified as ACGM2 according to HSE guidelines, for example a K12E. coli strain bearing a PBR322 plasmid (poorly mobilisable but not non-mobilisable) expressing a non-toxic gene product, are contained at the LSCC1 level; in the USA they would be grown at the less stringent GLSP containment level. In other words, an organism which poses a negligible risk to health and to the environment is categorised in the UK for the purposes of scale-up at the same level as pathogens such as Legionella spp, Neisseria spp, Clostridium botulinum, cytomegalovirus, influenza virus and herpes simplex virus.

It must be emphasised that the scientific understanding displayed by both sets of regulations are similar as are the mechanisms for assessing and dealing with the problem. The main difference is in the perception of the magnitude of risk versus the potential benefit to society. There would seem to be much less hesitancy about GMOs in the United States and their excellent safety record over the past twenty years suggests they have got the balance right. The current implementation of the UK GMO regulations is onerous, involving form-filling and time delays not experienced by our US colleagues. There is the potential in the new (1992) regulations on GMOs for this situation to worsen (depending on interpretation) when surely given the safety record of GMOs we should envisage loosening of the regulatory grip.

Dr Malcolm P Weir

Head of Protein Biochemistry

Letter to the Clerk from Professor Geoffrey Goldspink, Royal Free Hospital School of Medicine, University of London

I welcome this opportunity to submit written evidence for maintaining a strong biotechnology research base in the UK and the need to implement safeguards that take into account potential dangers to both human and animal health. The scientific community in Great Britain is now primarily looking to the Upper House to stress the need for a strong UK research base in molecular and cellular biology. The collective expertise of Sub-Committee II is impressive and I feel I may be only stressing points, of which the Committee will already be aware. I will make some general comments concerning the problems that retard the development of biotechnology in the UK and then highlight specific areas that are emerging and mention the kind of regulations that might be appropriate.

Although its start has been slower than some stockbrokers had anticipated, it is reasonably certain that the biotech industry will be one of the most important industries in the future. Julian Huxley in 1936 stated:

> **"Biology is as important as the sciences of lifeless matter and biotechnology will in the long run be more important than mechanical or chemical engineering".**

If there is not a series of incentives that involve university research departments as well as industry to increase biotechnology research, I regret to say that Britain will be left out of this development and progress yet further down the road to becoming a third world economy.

I. INTEREST IN BIOTECHNOLOGY

Approximately 10 years ago I took a position as Visiting Agassiz Professor at Harvard and whilst I was in Boston I took the opportunity to learn up to date research methods in biotechnology. Also whilst in Boston I was approached by Tufts University, New England Medical Centre, to help set up Basic Veterinary Sciences in the newly formed School of Veterinary Medicine. There I became Executive Director of the Peabody Institute where we established strong biotechnology and musculoskeletal groups. I visited Boston recently and the biotechnology group has gone from strength to strength, with over 20 well funded projects backed by pharmaceutical and biotech companies as well as State and Federal government funding. Virtually every State in the USA has established Biotechnology Institutes that are affiliated with a University.

I was then invited to return to the UK to establish biotechnology and molecular and celular biology teaching at the Royal Veterinary College. I became the Foundation Professor of Veterinary Molecular and Cellular Biology of the University of London and Director of Biotechnology at the Royal Veterinary College. I was successful in obtaining support from the Wellcome Trust who paid my salary for five years so this was essentially at no cost to the Veterinary College. This was however, in some ways a frustrating experience because of the mind set of an isolated veterinary college and the difficult funding situation prevailing in this country. In the States representatives from pharmaceutical companies visited the campus to find out what research was being carried out and to ask if we needed financial suport. There was also venture capital money from the banks and the University encouraged the patenting of any application of research that was commercially viable. Individual faculty members were induced to come forward with appropriate projects and rewarded using a simple formula for the royalties of; **a third** for the research worker(s); **a third** for the school and **a third** for the company who looked after the patenting and commercialisation aspects. The UK University has considerable resources in relation to expertise and creative science and I decided the only way to make an impact was to collaborate with other groups in London University system and other UK and EC Universities. By doing this I was able to get a good group of young research workers (four from Germany) and we did some very valuable work which will lead to the adoption of new methods of treatment and diagnosis in human and veterinary medicine. I recently took the Chair of Anatomy and Developmental Biology at the Royal Free which is now linked to University College London. Now that the Molecular Neurobiology Unit headed by Professor E. Barnard FRS (who is supported mainly by the pharmaceutical industry) has joined us, we have the critical mass to carry out biotechnology research in relation to human and veterinary medicine at the highest level.

II. GENERAL COMMENTS

Lack of public awareness and misconceptions related to biotechnology

It should be obvious that biotechnology research, which has its roots in this country, should receive strong financial support because of its potential benefits for mankind as well as its money-saving (see below) and wealth creating potential. Regrettably, the general level of scientific education in this country is low and the average citizen is more likely to regard biotechnology as the science of creating monsters, as he or she is unprepared to grasp the enormous benefits that will no doubt accrue from the application of recombinant DNA methods to human health care, animal health and production and cleaning up the environment. In the United States there is more venture capital available and industry is more accustomed to helping to maintain the US research base. In other countries the development of biotechnology is actively encouraged by financial support from government sources. Here in the UK we seem to be falling between two stools: the UK Industry seems to have no great incentive to support university research eg by tax write-offs, and there is no political capital to be gained if the government is seen to support research, particularly biotechnology research.

Transfer of biotechnology expertise abroad

For some time the UK scientific community has been concerned about the 'brain drain' and we have been told by some politicians that as many young workers come to the UK as leave the UK. It has been obvious however, that the calibre of young scientists leaving for the USA has far exceeded that of those coming here to do post-doctoral research. Professor Sydney Brenner who was the previous Director of the MRC Molecular Biology Laboratory, told me that virtually every person gaining a PhD in molecular biology over the last few years from this world-famous institute has gone to the United States. Many of these very able young people with the necessary skills for biotechnology research will not return because of the higher salaries and levels of research support in the United States.

My concern now also stems from the fact that many British laboratories are taking research students and postdoctoral workers from the Far East eg, Japan or Sinagpore because they come with their own, salaries. Indeed, in the present research grant climate this is often the only means of maintaining ongoing research. After learning the techniques in use in this country, they return, usually to government supported institutes and pursue the potentially wealth-creating projects in their own country. In contrast, the number of research studentships and post-doctoral fellowships for UK graduates is insufficient to enable all well qualified British students to receive a research training. Because of the weakening of the UK research base, companies such as Glaxo have stated that they may have to move all their research activities to other European countries or the United States. The previous government stated that university departments should be sponsored by industry. Where this has happened, it is important to note that the companies are usually foreign, eg, American companies have sponsored the pharmacology department and a part of the biochemistry department at Oxford and a Japanese pharmaceutical company has sponsored a new molecular neuroscience institute at University College London, in each case with rights to all of the data obtained. The British Technology Group, now that it has been sold off, seems to be promoting American more than British biotechnology (attached please find a copy of page from Drugs & Market Development).

As the transfer of information is essentially one way and for the other reasons mentioned above, I would predict that the biotech industry will flourish in the Far East and in the United States. The EC are trying to encourage the development of applied molecular biology but the bureaucracy is formidable and they deter original applications by prescribing too tightly, the areas of research they will fund. Also the EC requires several countries to be involved each time. Since companies generally are extremely wary of co-operations if other companies are involved, this in practice, means that one industrial partner (or more) must link with several diverse and far-flung academic laboratories which discourages initiative; hence good new approaches in biotechnology in the EC schemes are rare, as their panel members can testify. The SERC has too little money available to encourage a wide spectrum in biotechnology, while the MRC has no schemes in this field that would encourage industry to join with an academic group for a joint research project. A new initiative that would fund the latter enterprises separately from the two monolithic Research Councils would infuse much needed new life into the system.

Regulations for the biotechnology industry.

The regulations will hopefully, be formulated so that they protect the industry as well as providing the necessary safeguards. Adverse publicity surrounding any errors made when applying biotech methods could be very damaging. This would reinforce the average citizen's misconceptions and set the industry back several years by heightening consumer resistance to biotech products and creating a demand for more restrictive regulations. One other aspect that has given biotechnology a bad name is that some people, particularly in the States, established companies with exaggerated claims of promised products and sold the company before the product was available. In general, expectations have been unrealistic regarding the length of time it takes from inception to the marketplace. It seems that it is not possible to legislate against false claims ranging from fraudulent to overly optimistic except by relying on the present laws. At the risk of stating the obvious, the regulations must provide safeguards for human and animal life and address environmental issues. The balance is difficult to achieve as the regulations should not be too restrictive as to hamper the development of the molecular biology research base and the biotechnology industry in the UK.

III Areas of Biotechnology Development

Diagnostics. The first real impact of recombinant DNA technology has been to develop precise and cost effective method for the diagnosis of hereditary diseases and the presence of latent pathogens or pathogens at subclinical levels. Many of these tests now rely on the polymerase chain reaction (PCR) for which the American company, Cetus, owns the patent. This biotech company are now demanding that all diagnostic labs using this method should pay royalties even though DNA polymerase derived from thermophilic bacteria is available from several sources. The sensitivity of the PCR techniques means that a single gene copy can be amplified a million times within a couple of hours and this means that screening of early embryos can be carried out by removing a single cell at say the 64 cell stage. As an extension of the *in vitro* fertilization procedure, it is therefore possible to select the embryos that are to be reimplanted. This is usually viewed as acceptable for breeding cattle but not for human beings. The other social and moral issues which are also probably not within the remit of the Committee, pertains to the use of diagnostic procedures that may be used by potential employees and life insurance companies which will detect the presence of oncogenes and other DNA of viral origin of which HIV screening is already mandatory for prospective employees of some US companies.

Production of Biologically Active Peptides. Using specifically engineered genes introduced into bacteria and other cells it has been possible to produce human protein hormones cytokines, growth factors and clotting factors to treat a variety of diseases. Notable examples are human insulin for the treatment of diabetes in patients who are sensitive to animal insulin and human growth hormone for the treatment of pituitary dwarfs who previously could be treated only by using hormone prepared by collecting the pituitary gland from dozens of human corps. Factor VIII which is needed for the treatment of Haemophilia A can also be produced by recombinant DNA methods in eukaryotic cells but not in bacteria. The traditional methods which rely on the isolation of the protein from human tissue are associated with the risk of contamination with viruses and cytokines. Very pure tissue (including blood) products are expensive but there is a much greater demand now that the risks of contracting spongiform encephalopathies (Creutzfeld-Jakob and BSE) and HIV are now more fully appreciated. Unfortunately, the pharmaceutical companies are charging rather exorbitant prices for the recombinant DNA hormones and growth factors that it is unlikely that the NHS will be prepared to foot the bill. For example it is predicted that it will cost $50,000 to $100,000 per year for a patient with Haemophilia A with pure protein (please see attached page from Drugs and Market Development). This is a major concern of our Haemophilia Centre here at the Royal Free. One of the problems stems from the patenting of genes and their use. European laws differ from American patenting laws. The whole area of whether naturally occurring genes should be patentable, needs to be reviewed.

Molecular Pharmacotherapy. A revolution has recently ocurred in the worlds of pharmacology and neuroscience by the application of recombinant DNA technology to drug binding sites. This new era depends upon clones for receptors (from the brain, the immune system, and all the animal body systems) and for ion channels and for membrane transport proteins. By applying these clones, new classes of drugs will be discovered, and present blocks to successful and error-free drug therapy will be overcome. Britain is slow to wake up to this revolution. Classical drug testing is still the main technique of most pharmacology departments. There are only two or three laboratories in the UK public sector active in this entire area, in contrast to the far greater numbers abroad. This is an area especially suitable for industry—academic collaborations, which will involve chemistry departments as well as those in biological sciences. The biotechnology of drug development would lead, if fostered, quite soon to mutually financially profitable discoveries and to the solution of pressing medical problems. Smaller companies focussed upon drug discovery, which are a feature of overseas development, even in small countries, are lacking in the UK. A new initiative here is urgently needed, written so as to support specifically this crucial area of biotechnology.

Gene Therapy. Over 4,000 hereditary diseases have been documented some of which are progressive and eventually fatal and for which gene therapy offers the only prospect of treatment. Even in those that can be treated by aerosol inhalation, intravenous or intramuscular injection of the protein this is becoming prohibitively expensive for the reasons mentioned above. To introduce the DNA so the body produces the protein should be better from the patient's point of view as well as being much more cost effective. DNA would have to be prepared by companies and again patenting of genes including engineered genes and the cost of the DNA are issues that need to be addressed. The ethics of gene therapy is the province of the Clothier Committee. Whether or not a gene transfer procedure is effective and the benefit: risk appraisal must be responsibility of the medical profession or in the case of domestic animals, the veterinary profession. In Britain, these professions are very conservative and undue caution could retard the development and introduction of these new techniques in health care. One concern is the use of viral vectors to introduce the engineered genes. Retroviral and adenovirus vectors have been used in animal experiments to efficiently transfer genes into muscle for the treatment of muscular dystrophy and for cystic fibrosis. In addition to the risk of tumorigenesis which would only affect the individual, there is the risk of some recombination taking place that could possibly lead to a retrovirus (of which HIV is a member). Again this sort of consideration is probably not within the remit of your committee but it is important background information.

Transgenic Animals. Creating monsters is the way some tabloid newspapers usually refers to the production of transgenic animals. Indeed, an American group supported by the USDA have produced very heavily muscled, "Arnold Schwarzenegger" pigs by introducing a ski proto-oncogene construct which if nothing else, demonstrates the potential of the techniques. The production of transgenic animals in Europe will probably not be focused on improving food and fibre value of agricultural animals for some years because of the animals rights and environmental pressure groups. The exception to this is possibly the introduction of gene to improve disease resistance. On the research front, producing animals as models for human diseases, particularly now that the technology allows us to "knock out" the endogenous gene and replace it with an altered gene, opens up new doors. The furore over the "Harvard oncomouse" produced and patented by Harvard University, demonstrates well the commercial implications even for transgenic animals as research tools. Perhaps more contention will surround the production and maintenance of transgenic animals designed as factories for the production of biologically active proteins. Work in Edinburgh at the AFRC Institute of Animal Physiology and Genetics Research and at the Tufts School of Veterinary Medicine, Boston, has led to such genes as the human Factor IX gene and the alpha 1 antitrypsin gene spliced the lactoglobulin promoter being introduced into sheep, so that the protein products are expressed in the milk. The latter gene, the protein product of which is needed for the treatment of emphysema, is apparently giving good levels of expression. The production of these animals posses a new challenge for the veterinary profession who will be concerned with the welfare and exploitation of these animals and the medical scientists and clinicians who will be concerned with possible dangers resulting from viral and cytokine contamination as well as the efficacy of the protein products of these introduced genes. From the legalistic point of view the questions are:

1. Who owns the natural gene and does this extend to the engineered versions introduced into animals?
2. Can transgenic animals be patented, as in the United States?
3. How far should industry be allowed to go in producing transgenic animals which are, by definition, abnormal?

I trust that some of the points raised will be of value to the committee in formulating your recommendations regarding the future of biotechnology in the UK in relation to the rest of the global competitiveness. If you consider I can be of further assistance please let me know.

Professor Geoffrey Goldspink

Chair of Anatomy and Developmental Biology

Evidence from the Green Alliance

1. *What is your interest in biotechnology?*

The Green Alliance (GA) is an independent, non-profit organisation working on environmental policy. It was founded in 1978, and works to raise the prominence of the environment on the agendas of all the key policy-making institutions in the UK, to help improve environmental performance across the board, in Britain and internationally.

In 1986 a Green Alliance staff member came into contact with US commentators on the environmental risks of releasing genentically modified organisms (GMOs) into the environment. The Green Alliance considered that this was an issue that should be raised on the UK agenda, and organised a tour of key UK institutions and organisations for US campaigner Jeremy Rifkin. This included meetings with ACGM, with leading industry figures, with environmental risk specialists, with environmental pressure groups, and giving evidence to the Royal Commission on Environmental Pollution for their 13th Report.

After Rifkin's visit, the Green Alliance kept a watching brief on the issue. When the Environmental Protection Bill was introduced in 1989, the Green Alliance commented on the Part VI provisions for regulating GMOs, in particular the lack of provision for public access to information. In the spring of 1990, while the Bill was still progressing through Parliament, Julie Hill, then Parliamentary Officer for the Green Alliance, was asked to join the newly-formed Advisory Committee on Release to the Environment (ACRE) as a "lay" member ie, without specific scientific expertise. This appointment was one of the rare occasions on which someone with an environmental pressure group background has been asked to join a statutory committee.

Julie Hill still sits on ACRE. Since a large part of the Committee's remit is to comment on evolving legislation, she has a detailed knowledge of the development of both the primary and secondary legislation in this area, as well as knowledge of the scientific uncertainties involved in reglating GMOs. She has also been a liaison point for other environmental groups interested in the issues.

Recently the Green Alliance has put forward proposals to a number of interested parties, including industrialists, scientists, regulators, and pressure groups, to establish a forum for discussion of key issues in this area. These include the long term aims of risk assessment for release of GMOs; and the role of genetic modification in sustainable agriculture. These proposals have been welcomed in principle by some of the key figures in the field.

2. *How and why is biotechnology important to UK industry?*

We are not expert in the estimates of the potential market for UK biotechnology products, so we do not feel qualified to comment on this point. However, we would make the comment that from an environmental perspective, UK companies should be aiming to use biotechnology in applications that will benefit the environment, whilst at the same time avoiding the imposition of additional risks (see the answer to question 4 below).

3. *What future prospects and opportunities does the technology offer?*

In theory, it is clear that genetic modification and other biotechnologies could be environmentally beneficial, for instance by finding ways of cleaning up otherwise intractable wastes; by engineering crops that need less chemical inputs; by producing alternative feedstocks to fossil fuels. However, none of these applications has reached the market in the UK, and very few elsewhere, so it is difficult to judge their real usefulness. The thoretical opportunities are meaningless without the willingness to devote resources to developing them into products.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

The Green Alliance is primarily concerned with the risks of releasing genetically modified organisms into the environment. The risks are hypothetical, since no adverse effects have yet been observed from the comparatively small number of releases carried out in the UK and elsewhere. The Royal Commission on Environmental Pollution's 13th Report[1] gives one of the useful accounts of the possible nature of these risks. It discusses the possibility of genetically modified organisms showing unexpected competitive traits, and becoming established, and even becoming pests, in natural and semi-natural environments (4.2 and 4.14–4.29); the possibility of the genetic modification of viruses resulting in altered virulence or widening of host range (4.3); the possible danger of consumption of plants modified to express toxins by non-target organisms or humans (4.5); the spread of resistances to toxins engineered into plants (4.6); possible alteration of nutrient and water cycles through genetic modification of bacteria that play a key role in them (4.8 and 4.9); the spread of herbicide resistance for modified crops to weeds, making their control more difficult (4.10).

In our view, in the three and half years since this report was published, no evidence has become available that can make us confident that these possibilities can be discounted. We therefore support the continuation of a regulatory regime that includes requirements for risk assessments of all proposals to relase genetically modified organisms into the environment, and their case-by-case scrutiny by a statutory expert committee. We also call for thorough, long-term monitoring of the results of releases, and increased provision of funds for research into the functioning of the environment into which releases are made.

5. *Should biotechnology be regulated by an industry specific regime?*

We are unclear as to what is meant by "industry specific regime". In our view, all work with GMOs should be regulated for human and environmental safety, including contained uses and release to the environment. This will include regulating academic institutions and a range of companies.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

We are not clear what is meant by "a technical point of view", ie whether this refers to the technicalities of the legislation, or the technicalities of the technology. Either way, the question poses a false dichotomy. To start with, horizontal regulation on GMOs does not entail judging a product through the process by which it is derived. It simply means that any application of the process acts as a trigger for scrutiny, whether it is at experimental stage and totally unrelated to a product, or at market stage. It does not imply that *any* application of the process is dangerous, only that the process may result in the experiment or the product posing risks, and that these risks should be assessed and the assessment checked by regulators. This means that any given product will indeed be judged by its specific characteristics; these will to some extent be an upshot of the process by which it was derived.

A vertical system of regulation for different types of product can incorporate judgment of the risks that might result from the fact that it is genetically modified. However, product clearance systems alone, certainly the UK and also in Europe, are not sufficient to cover all the possible applications of genetic modification. In particular, they cannot account for experimentation, a proportion of which is not related to a specific product development, and which could be considered to carry greater risks than products that are nearing the market and have already been through extensive trials.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

Only if adequate risk assessment procedures are put in place. There is the possibility of duplication of expertise if several different product clearance systems ie pesticides, pharmaceuticals and food, all include expertise capable of judging the risks of the GMO aspects of the product. In practice it will be easier for those systems to refer products to one committee, like ACRE, as presently happens under the horizontal regulations. Since, as noted above, a vertical approach will not be able to take account of experimentation, such a committee will need to exist anyway.

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[1] The Royal Commission on Environment Pollution: Thirteenth Report: The Release of Genetically Engineered Organisms to the Environment. July 1989 Cm 720.

8. *How do current regulations compare with those of other competitor countries, in Europe, in the Far East, in the USA?*

Since the UK regulations implement EC directives on contained use and deliberate release of GMOs, the situation in the UK and other EC member states will be broadly similar. In the USA the situation is still in flux. We do not have expertise on the situation in the Far East. Green Alliance work on environmental strategies in other countries has demonstrated that cross-cultural comparison of regulatory regimes is very difficult, since the effects of regulation very much depend on how it is applied by regulatory agencies, and on the political culture under which it is operating. The most frequent comment about GMO regulation from all countries that have such rules is that their regime is particularly restrictive, and is disadvantageous to industry vis a vis competitors.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards: research, product development, investment, location, sales and marketing?*

We are not qualified to comment on this, but would suggest that it will be very difficult to quantify with any accuracy given the still uncertain regulatory climate in many other countries.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British Industry of research conducted in the UK science base?*

We are not qualified to comment on this point.

11. *How can the issues of public acceptance be addressed?*

The industry must show that it understands the basis of the regulatory regime for release of GMOs, and accepts the need for it. It must co-operate with the statutory registers of information by providing as full documentation as possible, with minimal exclusions on grounds of commercial confidentiality, and should also provide information directly to the public if asked. It must admit to the areas of scientific uncertainty that make risk assessment difficult. It must be able to demonstrate the environmental and other benefits of the technology, not just put them forward as possibilities. It must be willing to engage in dialogue with public interest groups.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

The international community has been discussing the need for an international regime to regulate release to the environment of GMOs for more than three years, and the possibility of establishing such a regime formed part of two of the outputs of the UN Conference on Environment and Development (UNCED): the Biodiversity Convention and Chapter 16 of Agenda 21. If such a regime was put in place, this might provide the "level playing field" that the industry often says it needs to overcome threats to competitiveness.

Evidence from Don Grierson, Professor of Animal Physiology, University of Nottingham

SUMMARY

Plant biotechnology makes it possible to generate novel plant varieties with greater speed, efficiency, and precision than hitherto. It is likely to have a major impact on our ability to change and manage renewable natural resources. There are safety issues but these can be readily addressed. Horizontal regulation for plant biotechnology is unsound. Regulations in the USA may be less cumbersome than in Europe. There is a need to better inform the public about plant genetic engineering. Basic research should be strengthened in order for the UK to take full advantage of the technology in the future.

1. I am a Professor at Nottingham University with teaching and research interests in plant molecular biology and biotechnology. I am also Head of the AFRC Research Group in Plant Gene Regulation and from time to time act as a consultant to UK companies with interests in plant biotechnology.

2. Plant biotechnology and the fundamental research that underpins it makes it possible to improve our basic understanding of how plants work and to use this knowledge for plant and crop improvement by both traditional and novel methods. New plant varieties (transgenic plants) have been generated by this technology which are resistant to insects, viruses, and herbicides. Others have improved nutritional value, shelf life, and processing characteristics for the food industry. Plant biotechnology makes it possible to do such work with speed, efficiency, and far greater precision than previously. It also makes it possible to accomplish improvements that were not possible by traditional methods. Once made, the changes are inherited genetically and repeated treatment of the plant is unnecessary.

3. Plant biotechnology is likely to have a major impact on production of food and other plant based raw materials, permit the production of novel materials in plants, and has the potential to have a beneficial effect on the environment by lowering inputs of agrochemicals. In a general sense, the likely rate of improvement of knowledge and technology will mean that our understanding of and ability to change and manage renewable natural resources will be transformed over the next few decades.

4. The production of new plant and animal varieties by traditional methods of breeding and selection has always been associated with potential hazards. It is well known that some existing non-food plants are poisonous; that pests, diseases and environmental conditions can render food crops poisonous; that introduction of "foreign" species into particular eco-systems can have adverse consequences; that the applications of chemicals to aid plant and animal production can generate health risk. Hazards of this type may also be associated with crops generated by the new methods of biotechnology and the same rigorous testing and vigilance will be necessary. There are three areas where biotechnology could be argued to pose *new* hazards. Firstly, the method(s) for generating them could endanger those producing them or eating them. This question is relatively easy to address. It is covered by existing legislation and there is sufficient existing knowledge to conclude that for several methods there is no risk. Secondly, the genetic modification made by a biotechnological process might have unexpected consequences in the organism, rendering it dangerous, unpredictable or toxic. This is unlikely, since much of the change element associated with traditional breeding and selection is eliminated. Thirdly, the generation of a novel variety might have an unexpected adverse impact on the environment. This possibly is not unique to varieties generated by biotechnology, but the scope for potential problems could be increased. The potential hazards posed by the second and third possibilities can be addressed by rational scientific analysis of the change made and trials and tests on the new varieties. It could be beneficial to involve those with experience in nutrition, toxicology, and ecology when such potential hazards are assessed.

5. Biotechnology can involve, among other things, (i) the growth of animal cells in culture to produce compounds of use in the pharmaceutical industry, (ii) the utilization of genetically manipulated bacteria and fungi to generate processed foods by existing or novel methods, (iii) the production of transgenic plants (or animals) with altered properties for production of fresh or processed foods or raw materials. These activities are diverse and raise different questions of safety, ethics, and environmental impact. However regulation is managed, sufficient thought should be given to ensure that all areas are addressed with equal authority and vigour.

6. Horizontal regulation is unsound. This is because a method for producing a transgenic plant may be safe, but the gene(s) introduced may bring about a change that generates a variety that is toxic. Thus, using the same general method, or process it would be possible to cause either a beneficial or hazardous change, depending on the gene(s) transferred to the transgenic plant. There *is* a need to consider the processes used to generate transgenic plants. There are several, and it should not be difficulty to decide whether they are safe or not (most if not all are safe in my opinion). Thereafter, it will still be necessary to consider the characteristics of the variety—see (4) above.

7. Horizontal regulation should be addressed quickly for plants; it is probably a non-issue at least in some cases. Vertical regulation is more important.

8. European regulations appear to be muddled, restrictive, and difficult to operate across the EEC. I have no experience of the far East. The regulations in the USA appear clearer and easy to operate, judging from what American colleagues tell me.

9. (1) Research is more difficult, expensive, and time consuming because of the existing regulations.

(2) Similar comments apply to product development.

(3) —

(4) —

(5) I know of one major development in plant biotechnology being marketed first in the USA. There are two reasons for this: firstly, it is a large potential market; secondly, the regulations are more "friendly".

10. I have a general feeling that the present regulations are cumbersome, expensive in time and money, and not as helpful as they could be. However, I have no experience from the industry side. It is clear to me, however, that the current regulations for work with transgenic plants slow the pace of research in Universities and make it so expensive that some potentially pioneering work is just not done.

11. There is a need to improve the general eduction of the public. People appear to be frightened by the concept of "genetic engineering". This is largely out of ignorance of what it involves. The situation is often not ameliorated by the newspapers and television. It seems to me that UK companies could do much more. The best place to mount an eduction programme is in the schools. Public acceptance would be more likely if it was clear that they were going to get a product that is better, safer, or cheaper than existing ones.

12. Plant molecular biology and biotechnology really are revoutionising our understanding of plants and how to manupulate them. There is a great need to improve our fundamental understanding of plant physiology, biochemistry and genetics in order to take full advantage of these opportunities. These research

areas need to be strengthened in selected UK universities. Measures that improve the research interaction between Institutes and Universities on the one hand and Industry on the other would be beneficial.

Evidence from John B Harris Professor of Experimental Neurology Newcastle General Hospital

Q.1 *What is your interest in biotechnology?*

(a) I direct a Laboratory concerned with the diagnosis, management and treatment of patients with inherited diseases of muscle, and have a close interest in other degenerative diseases of the nervous system. There are good reasons to believe that many of these conditions could be managed better if damaged genes could be replaced by or supplemented with normal genes introduced into the damaged tissue or cells.

(b) I have a direct interest in toxins present in the venous and poisons of dangerous snakes, spiders, scorpions and related species. The toxins are of interest for many reasons, but two reasons might be highlighted—the development of novel and specific insecticides (achieved by incorporating the genes encoding insect-specific neurotoxins into plants destroyed by insect predation, or by incorporating the genes into insect-specific viral genomes) and the generation of non-toxic homologues of the toxins. If this latter could be achieved by manipulation of the gene encoding the toxin, that gene could then be incorporated into a bacterial expression system, and the non-toxic homologue could be used to raise neutralizing antibodies targeted against the toxic homologue. The therapeutic advance could be very important to impoverished developing countries which lose many productive workers to incidences of natural poisoning.

Q.2 *How and why is biotechnology important to UK industry?*
and

Q.3 *What future prospects and opportunities does the technology offer?*

It is important because it has already been shown to be significant in the development of natural products in large amounts (Human insulin for example), in the enhancement of agricultural output, in the production of vegetable and other non-animal protein by large-scale fermentation and the utilization of natural toxins as a source of a wide range of useful biological products.

Q.4 W*hich developments in biotechnology raise issues of safety and how should they be addressed?*

Viruses and bacteria are increasingly being used as 'vectors' to carry normal copies of genes into cells and tissues. A good example is the interest shown in the use of adenoviruses to introduce a normal 'dystrophin' gene into the muscle cells of patients with muscular dystrophy—diseases in which dystrophin is either totally missing or present in only small amounts. There are two potential problems with this approach. The first is that many adenoviruses are non-specific and cannot be targetted directly to the tissue of interest. The second is much more important. The viruses used for this purpose are unable to replicate because a large segment of their own DNA has been cut out to allow the insertion of 'dystrophin' DNA. The viruses will remain unactive provided they have no contact with wild type viruses. If they have contact, DNA recombination could occur and the viruses allowed to replicate. They could, in such circumstances, be highly pathogenic.

Insect-specific viruses have also been used as potential vectors of DNA coding for toxic proteins. The idea is that the release of such engineered viruses could be used to carry insect-specific neurotoxins to insect pests. The problems are similar. Most viruses, though insect-specific are not very selective between insect species. Thus beneficial as well as pest species are at risk. There is also the danger that the engineered virus activated by contact with wild-type virus, could have lost its insect-specific nature and infect non-insect species.

Q.5 *Should biotechnology be regulated by an industry specific regime?*

I'm not sure but suspect yes. There are important potential problems involved in the use of micro-organisms where the safety issues can be clearly identified. I cannot imagine that a single set of regulations could cover the clinical use of viral vectors in a very controlled environment, and the widespread use of vectors in agricultural practice. Other issues that would require different guidelines are those nvolved with genetically modified live stock. For example, the application of biotechnology to enhance growth rate or milk production or hormone production in animals raises serious moral issues that *must* inform the development of regulations.

Q.6 *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)? and*

Q.7 *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

I favour vertical regulation, but there are good reasons to believe that both horizontal and vertical will be necessary. I can offer no "expert" opinion.

Q.8 *No comment.*

Q.9 *No comment.*

Q.10 *No comment.*

Q.11 *How best can issues of public acceptance be addressed?*

The most significant problem of public acceptance is the low level of scientific literacy in the general population. The simple result of this lack of literacy is that much information is misunderstood and public opinion is based more on emotion than on balanced judgement.

Government Departments, the Research Councils and the major Medical Charities could influence public opinion by preparing or commissioning the preparation of articles for the popular press. Major industrial organisations should be stimulated to prepare similar pieces identifying major successes, for example, in the preparation of better and safer products such as insulin. Even the brewing industry could point out the value of biotechnology. Emphasis might be placed on the potential value of the application of biotechnology to plant production.

Genuine concerns of the public, and of pressure groups, over the application of biotechnology to enhance the production of milk or low-fat meat-animals should be confronted openly and honestly. It is unfortunate that Government and the Civil Service is now considered to be secretive and economical with the truth by such a large section of the general public.

Q.12 *What other factors do you consider will play a crucial role in competitiveness of the UK biotechnology industry?*

Investment. Much novel work in this field will be made by small, high specialized companies with a large ratio of skilled/unskilled workers in the workforce. The research is long-term and needs investment that takes into account both the high-risk and long-term nature of any return. Britain is desperately bad at making such investments. We run a continuing risk of losing novel work as a result. I believe this to be more important than over-regulation.

Evidence from Hoechst UK Limited (Dr C M Macdonald, Head of Drug Development)

Q.1 *What is your interest in biotechnology?*

As Head of pharmaceutical research laboratory I am naturally interested in the discovery development and commercialisation of new medicinal products. As a company, Hoechst is committed to realising the full potential of biotechnology in its widest context as we recognise that it offers a great many opportunities for scientific advancement not only in medicine but also in veterinary science, crop protection and other related disciplines. Several products from our biotechnology research have already achieved regulatory approval.

Q.2 *How and why is biotechnology important to UK industry?*

Historically, the UK has been recognised as a country of scientific excellence with a tremendous record of innovation. This has encouraged investment from the industrial sector particularly by large international pharmaceutical companies. In the future, however, economic and political pressures will force companies to review their investment strategy. It is likely to be countries which encourage and foster the development of the scientific base with new technologies like biotechnology that will benefit from this. If the UK is to continue to gain economically from a strong science base it must ensure it does all it can to encourage new technologies like biotechnology.

Q.3 *What future prospects and opportunities does the technology offer?*

Biotechnology offers the possibility of developing a whole range of new beneficial molecules. In the health care industry this will include not only the provision of improved medicines for man and animals but also new diagnostic techniques which will enable a better understanding of disease processes to be achieved. Agriculture will also benefit from new safer and more selective products and from new crop types.

Biotechnology is presently at the cutting edge of science and is therefore likely to attract the most capable of our young scientists and technologists. They will move to wherever this work is conducted.

Q.4 *Which developments in biotechnology raise issues of safety and how should they be addressed?*

It is right that issues of safety should be considered about any new technology or industry. Public debate must however be conducted in a rational and non-emotive way and every attempt should be made by our legislators to ensure pragmatic, realistic solutions. To date biotechnology has an excellent safety record and public concerns about safety remain quite unfounded. Much legislation already exists to cover safety evaluaton of new products. Questions about safety should be considered on a product by product basis and should be considered in light of results from appropriate safety evaluation studies.

Q.5 *Should biotechnology be regulated by an industry specific regime?*

Biotechnology is not a single industry and the procedures used will vary greatly from the simple to the highly complex. The existing legislative framework for the difference industries involved should, perhaps with minor modifications, be capable of embracing all aspects of biotechnology.

Q.6 *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regualtion (where a product is judged by its characteristics)?*

Q.7 *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

Products should only be judged on a case by case basis by their characteristics and not by their processes.

Q.8 *How do current regulations compare with those of other competitor countries?*

There is concern that some European legislation on biotechnology and its processes is over-restrictive, bureaucratic and inflexible in its implementaion. It is a matter of public record that Hoechst has been greatly effected by this at its main plants in Germany.

Both Japan and the USA appear to have taken a much more enlightened approach to biotechnology, where government attitude appears to be more supportive and aware of the considerable benefits to be achieved.

It is therefore important that legislation in the UK, whilst ensuring that adequate safeguards are put in place, is not unnecessarily restrictive, but is based on a pragmatic and flexible assessment of benefit and risk.

A positive political environment is crucial to further investment in the UK.

Q.9 What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry?

Research

Much research, particularly in academic institutes, is curiosity driven. Any regulations which greatly increase costs and bureaucracy will have a considerable impact on this work and will drive away both investment as well as our more able scientists.

Product development

Product development, particularly for pharmaceuticals and agrivet products, already has an effective framework for assessing the quality, efficacy and safety of products. Any new legislation should not add further to the time and cost of such programmes.

Investment and Location

A sympathetic political and legislative environment will facilitate investment in the UK. A highly restrictive and cumbersome legislature will do exactly the opposite.

Q.10 *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

The reduced level of funding and poor underpinning of the science base within education in the UK is already a cause for concern to industry. Any legislation which further handicaps new technology will surely have a detrimental effect on investment and commercialisation in the UK, and will inevitably lead to economic exploitation being carried out elsewhere.

Q.11 *How best can issues of public acceptance be addressed?*

Public perception of science and the industries involved with it is probably at an all time low. Biotechnology, because it is new and is as yet poorly understood by the public, has created its own particular and largely irrational fears. It will take considerable time and effort to overcome this. It is important that there is an open public debate which emphasises the potential benefits, both scientific and economic, to be gained by such new technologies. Concerns about safety must be addressed but such discussions should be carried out in a rational and non-emotive way.

Inevitably, we will probably have to wait until there is more familiarity with this new industry and its products, and that there is sufficient historical evidence of its safety before there is widespread public acceptance.

In the meantime there needs to be a willingness by government and its agencies, the science based industries and any other parties with an interest in this field to work together to promote biotechnology and the science base more generally within the country.

Q.12 *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

It is important that protection of intellectual property rights is safeguarded for the inventor and that new products are given adequate patent protection if the considerable investment which is required in this area is ever to be recovered.

Biotechnology, and the products to be derived from it, should be seen as an opportunity for the UK to reinforce its manufacturing base within the high-tech industries. Government and its agencies should therefore work closely with industry to ensure its future success. This should include direct funding where appropriate, or providing enabling procedures whereby funding is more easily available. The general promotion of science and technology within education would have a less tangible but ultimately more sustainable effect on the future of this industry.

Letter to the Clerk from Hoechst Aktiengesellschaft

In your letter dated 24 February 1993, you requested answers to eight questions concerning our experience with the biotechnology regulations in Germany. I hope that the following reply will provide you with the requested information.

1. *How important does your Government perceive biotechnology to be?*

Biotechnology is supported since approximately 1978 through various programmes. The most recent is the Biotechnology 2000 Programme by the Federal Research Ministry (BMFT). Because of the concerns expressed at a joint hearing of the health and research committees of the German Parliament (Bundestag) in February 1992, currently the existing Gene Technology Act is being amended. All major political parties of the Budestag have expressed their support to introduce simplifications to the Act. This also applies to undertake effort to amend the EC-directives 90/219 and 90/220.

2. *Which developments in biotechnology are thought to raise safety issues?*

The Gene Technology Act as well as the EC-directives unfortunately are based on the assumption, that gene technology needs specific regulations (process orientation), which in the US and Japan more adequately products are assessed in respect to their properties (product orientation). Safety issues may concern pathogenic organisms, the release of organisms into the environment and "non-biological" risks which may result from increased "knowledge", eg by the application of diagnostic procedures to protect workers (with potential consequences on employment/non-employment) or "misuse" in respect of abortions.

Organisms can be distinguished into non-pathogenic and pathogenic organisms in respect to man, animals, plants etc. It is obvious, that operations with pathogenic organisms need adequate education and safety precautions (eg research with the AIDS-virus) not only when using recombinant DNA methods but also in classical biochemical or virological laboratories. By contrast, from both a theoretical view and from practical experience, the genetic modification of harmless non-pathogenic organisms like bakers yeast or E. coli K12—with recombinant and classical techniques—does not convert these organisms into pathogenic ones. Similarly, the release of natural "exotic" organisms into foreign environments may cause some damage (examples are known) while the release of genetically modified plants like tomatoes or potatoes does not lead to their uncontrolled growth in the European environment. In respect to the use/misuse of diagnostic procedures, a new quality of problems does not arise—only the quantity of traits which can be diagnosed will increase. In this respect, the classical diagnostic procedures should have been regulated in the past.

3. *In your country, is biotechnology regulated by a specific regulatory regime?*

Yes. From 1978 until 1990 recombinant DNA operations in "contained use" were covered by the "Gene-guidelines" issued by the research ministry. Since 1 July 1990, the federal Gene Technology Act and various statutory regulations regulate any recombinant DNA operation for research, commercial use and deliberate release.

4. *Do regulations distinguish between contained use and general release (for experiment or marketing)?*

Yes. The Gene Technology Act fully transforms the EC-directives into national law including the marketing provisions.

5. *Is regulation in your country "horizontal" or "vertical"? Which is preferred by your Government.*

The Gene Technology Act fully transforms the "horizontal" approach of the EC-directives into national law. Germany had voted in the Council of Ministers for these EC-directives. Hence at that time (early 1990) the German Government obviously was in favour of a horizontal approach. However, this position was not unanimously agreed by all ministries, and today it is questionable, whether this position is still valid. There is the clearly expressed will to amend the EC-directives and full recognition of the experience made in the US and Japan with their vertical systems.

6. What are the consequences of your country's regulatory regime on the competitiveness of your firm, in particular as regards (1) research, (2) product development, (3) investment, (4) location and (5) sales and marketing?

On constitutional reasons and particularly the federative structure of Germany, the Gene Technology Act is executived by more than 20 state authorities (Regierungspräsidien) with varying experience which led into different administrative procedures. A group of experts of the federal states (Länder) has been set up in order to negotiate and establish common procedures in the execution of the law. Authorizations for deliberate releases must be obtained from the Federal Health Institute (Bundesgesundheitsamt). Until today, there have been mostly negative experiences with the Gene Technology Act at the Hoechst locations which are in the state of Hesse. In particular, our experiences apply to basic research, development of processes and products and authorization procedures for production facilities, as the following examples shall indicate.

— Our laboratories which were registered under the Gene-guidelines in safety level two (1990–1986) may only be used for operations with non-pathogenic organisms (safety level one) even though the equipment has not changed. A comprehensive, lengthy and costly approval process is requested by the authorities if we want to operate the laboratories in safety level two under the Gene Technology Act. Hence research projects were shifted to other places.

— Pilot plants/experimental upscaling facilities can only be approved as production facilities (interpretation of the Hesse authorities of the "small volume" definition of the EC-directive 90/219; this is handled differently in other federal states). Any modification or new product development would require additional approval procedures with additional costs and would furthermore allow "professional" public opponents to gene technology to object and delay developments by going to court. Consequently, several potential recombinant products we now develop in facilities in the US, Japan, Australia and France with investments being directed into the respective facilities (eg more than 50 mio DM to Japan). Since these facilities are modern and therefore competitive, it is very likely, that future projects will be run also at these places. It must be understood, that the application of recombinant DNA technology is only a relatively small but essential part in product development which embraces microbiology, protein chemistry, toxicology, engineering, fermentation technology etc exercised by the respective scientists, technicians and external services. Therefore, the issue of employment may not be underestimated.

— While the EC-directives and the Gene Technology Act foresee two and three months periods for the granting of authorizations, in practice we are facing approval times at an average of eight-12 months (the time needed before the files are accepted by the authorities and declared complete usually amount to some additional months). In addition, it is certainly worth mentioning that the German regulations usually do not allow to start the construction of facilities and receive the permission of operation later (usually we need a permission for both the construction and the use of a facility first). A change is now proposed for the amended Gene Law in order to save time.

7. *Is biotechnology publicly accepted in your country?*

The answer is yes and no. Medical research and the production of pharmaceuticals must be considered as accepted. Many beneficial applications for improving processes or the replacement of chemical processes by environmentally friendlier biotechnical processes are more or less completely taken for granted by the media and the public and, therefore, not critically viewed. Agricultural applications for the production of renewable raw materials (oils, fibres, starch etc) seem to be acceptable, but the potential of producing recombinant food or using recombinant substances as food additives, has provoked great attention by the "classicial" opponents of biotechnology, part of the media and some consumer organizations. Interestingly, despite a complete lack of data on the properties (contents, flavour, taste, shelflife etc) of eg recombinant vegetables in Germany, all opponents pretend to have information and hands-on knowledge about the "health-risks" associated with such products.

8. *Has your Government implemented EC Commission Directives 90/219 and 90/220. If so, how? If not, when do you expect to do so?*

The Gene Technology Act came into effect on 1 July 1990. It fully implements the EC-directives via a combination of Law and Statutory Regulations; some of these still have to be enacted. As stated above, currently the Gene Technology Act is to be amended. It is questionable, if a workable and truly competitive Gene Law can be developed respecting the limits provided by the EC-directives. The problems with those were foreseen by both academia and industry and were unfortunately completely ignored by the Commission. It is very offputting to see that further regulations based on the existing EC-directives 90/219 and 90/220 are being developed.

I hope that the answers to the eight questions will be of help to the Sub-Committee.

D. von Winterfeldt Dr D Brauer

Letter to the Clerk from Dr J Winter and J v Manger-Koenig, F Hoffmann-La Roche Ltd

Thank you for your letter of 24 February 1993 which you sent to Dr Stefan Ryser. We welcome your efforts to assess the impact of regulation on the biotechnology industry by also using experience gained in other countries. You are aware that regulatory arrangements in EC countries are a direct result of the EC Directives 90/219/EEC and 90/220/EEC. These Directives do not only have a direct influence on EC Member States, but they are also of great importance to non-EC countries like Switzerland. The biotechnology regulations in our country are currently in the legislative process.

We can answer your questions as follows:

Q.1

How important does your Government perceive biotechnology to be?

It is our impression that the Swiss government perceives biotechnology as a key technology which is vital for our research and our industrial competitiveness. However, in the current political debate the influence of vocal pressure groups often leads to a situation where the actual and potential benefits are put into perspective with exaggerated alleged risks.

Q.2

Which developments in biotechnology are thought to raise safety issues?

Safety issues are discussed concerning research/production, the deliberate release into the environment of genetically modified organisms and biotechnology products.

Q.3

In your country, is biotechnology regulated by a specific regulatory regime?

The currently discussed proposals foresee the implementation of specific rules for genetically modified organisms into already existing general laws on environmental protection as well as health protection ("Umweltschutzgesetz", "Epidemiengesetz").

Q.4

Do regulations distinguish between contained use and general release (for experiment or marketing)?

Yes.

Q.5

Is regulation in your country "horizontal" (where a product is judged through the process by which it is derived) or "vertical" (where a product is judged by its characteristics)? Which is preferred by your Government?

The laws mentioned under Question 5 are "horizontal" since genetically modified organisms will be regulated as such. This is in accordance with Directives 90/219/EEC and 90/220/EEC. The second part of the question cannot be answered.

Q.6

What are the consequences of your country's regulatory regime on the competitiveness of your firm, in particular as regards

(1) research

(2) product development

(3) investment

(4) location

(5) sales and marketing?

(1) A regulation based on the EC Directive 90/219 will bring additional obstacles for contained use projects for research purposes (Type A operations) with low risk (NIH risk levels), eg, longer waiting periods, additional bureaucracy.

(2) Delayed product development

(3), (4) and (5) Questions cannot be answered yet as they depend on the future regulatory implementation.

Q.7

Is biotechnology publicly accepted in your country?

There is a public debate on biotechnology with some fundamentalists opposing the technology as a whole. The public discussion is focusing on biotechnology patents and on food produced by biotechnology methods. However, public acceptance is slowly increasing with the understanding of the benefits, especially in the health sector.

Q.8

Has your Government implemented EC Commission Directives 90/219/EEC and 90/220/EEC if so, how? If not, when do you expect to do so?

The Swiss constitution was amended by a referendum held in May 1992 which calls for appropriate regulations for genetic engineering. It is planned to amend the laws mentioned under Question 3. The time horizon is still open. As the Swiss people rejected to participate in the European Economic Area in December 1992 the two EC directives will not be implemented per se.

Evidence from IPMS

1. The Institution of Professionals, Managers & Specialists (IPMS) is the trade union which represents 90,000 scientific, technical and specialist staff in the civil service, related public organisations and an increasing number of private sector companies.

2. This evidence is based on comments from members in the Patent Office, Science and Engineering Research Council (SERC), Agriculture and Food Research Council (AFRC), Royal Botanic Gardens (RBG Kew), and Ministry of Agriculture Fisheries and Food (MAFF). The answers to question 1 are given separately for each area, as are answers to other questions where the source is clearly relevant to the comment.

Q.1 *What is your interest in biotechnology?*

AFRC

3. AFRC Institutes are involved in research to advance knowledge through which UK industry can explore new biotechnology options in product manufacture, quality control, safety regulation and energy efficiency.

R.B.G. Kew

4. RBG Kew is not itself primarily concerned with biotechnology business. Its mission statement and responsibilities place it firmly in the research base, especially with respect to plants. However, biotechnology impinges significantly on its activities in two main ways. First, the expanding range of scientific techniques broadly associated with biotechnology are and will be used, whenever appropriate, to further their aims in basic research and conservation; eg, various gene amplification techniques, possibly using microorganisms, in studies of plant molecular biosytematics and reproductive biology, and tissues culture to multiply rare and endangered plant material. Second, research on Kew's plant collections continues to reveal novel and useful traits in a wide range of plant species; and at least some of these may be exploited by organisations such as drug companies, for example, using biotechnological processes directly. With its commitment to responsible utilisation of the plant kingdom, Kew welcomes properly constituted links with biotechnology companies, and would not wish to see the industry unnecessarily fettered by regulation. Nor would they wish to see prohibitive restrictions and fees attached to the properly controlled and contained use of "biotechnological" techniques in their own laboratories.

MAFF

5. MAFF laboratories have a variety of interests in biotechnology and/or genetic manipulation. At the Central Veterinary Laboratory (CVL) the active molecular genetics unit uses biotechnology techniques to diagnose, study the pathogenisis and prevent disease. The Veterinary Medicines Directorate licences biologicals and both groups input to the MAFF policy group on genetic manipulation.

SERC

6. Biotechnology is an important new industrial technology. It offers significant opportunity for wealth creation across a number of individual sectors—many of which are UK strengths, such as pharmaceuticals and fine chemicals. It also offers the potential for environmentally cleaner production methods, remediation of past pollution and waste treatment. If these opportunities are to be taken a continued availability of new knowledge and techniques is required from the science/engineering base. Associated with this aspect is the requirement for trained and skilled personnel to utilise the new knowledge in commercially viable processes and plant. SERC, along with other Research Councils and Government Departments plays an important role

in these respects. Ultimately, however, the rate of development and exploitation of this technology will depend on the regulatory framework and issues of public acceptance.

The Patent Office

7. The role of the Patent Office is to facilitate the growth of industry and commerce through the establishment of intellectual property rights. As an Executive Agency of the Department of Trade and Industry it pursues this role through its work on maintaining and improving the domestic and international framework of protection for intellectual property, and through the administration of its statutory responsibilities. In the case of patents the statutory responsibilities are laid out in the Patents Act 1977, as amended by the Copyright, Patents and Designs Act 1988 and the Patents Rules.

8. A patent is a monopoly right to the exclusive use of an invention, in exchange for a full disclosure so that other people can use the invention after the patent expires. The current length of time that a patent may last is 20 years, providing renewal fees are paid.

To be patentable an invention must be:

(i) new

(ii) involve an inventive step

(iii) be capable of industrial application

(iv) not be excluded.

Excluded inventions include discoveries, scientific theories, aestetic creations, presentation of information, and computer programs.

9. More importantly for those involved with biotechnology, it is not possible to obtain a patent if the invention relates to a new plant or animal variety; or a method of treatment of the human or animal body by surgery or therapy; or a method of diagnosis; nor if the publication or exploitation of it would generally be expected to encourage "offensive, immoral or anti-social behaviour". The relevance of the latter clause will be demonstrated later.

10. Certain plant varieties may be protected in the United Kingdom under the Plant Varieties and Seeds Act 1964, but the Patent Office does not deal with this. Patents valid in the UK may also be obtained under the European patents Convention (EPC) which uses similar principles for deciding whether an invention is patentable.

11. Biotechnology has moved rapidly since the introduction of the 1977 Patents Act, and this had raised important questions over the patentability of some of the new technology available.

12. The patents legislation as it stands already contains some controls over what is patentable by the biotechnology industry. How the patents legislation relates to new technology with respect to what is patentable is still under debate. A major factor in this debate will undoubtedly come from increased public awareness and pressure on issues such as the morality of the inventions being patented and their impact on the environment.

13. Some detailed examples of the problems raised in the patenting of biotechnology are given under questions 4 and 8, although their separation into those sections is slightly artificial.

Q.2 & 3 *How and why is biotechnology important to UK industry? What future prospects and opportunities does the technology offer?*

14. Our members in AFRC and MAFF respond that Biotechnology can improve competitiveness and economic performance by:

- Replacing energy intensive production methods with low energy bioprocessing e.g. in fats and oils processing, plastics technology
- reducing production of toxic waste
- providing new low cost waste management technologies
- increasing the range of products in industry's portfolio
- providing more effective vaccines and new therapeutics.

15. Against a background of more stringent surveillance of new food processes and additives, biotechnology provides "nature-identical" technology and compounds. Genetic manipulation of food, plants and food fermentation microbes can increase production efficiency, product shelf life, flavour impact and resistance to spoilage/pests in primary production.

16. Trading competitors are actively developing industrial processes and products based on biotechnology, which will compete with existing technology and products on price and quality. UK industry needs biotechnology research to compete on equal terms. The chief source of competition is likely to be Japan and the USA based on current overt research activity.

Q.4 *Which developments in biotechnology raise issues of safety and how should they be addressed?*

17. Our members in SERC argue that the main issue, from a safety and a public concern point of view is that of "genetic engineering" (ie the use of recombinant DNA technology) to create new or altered organisms, plants, foods and products. It is important for the public to realise that much biotechnology does not require or utilise "genetic engineering". However, many of the potential advances that could be made in the areas of healthcare and agriculture may well depend upon recombinant DNA technology.

18. Similarly our Patent Office members record that advances in the field of biotechnology have resulted in the possibility of curing genetically based diseases, for example multiple sclerosis. Applications for DNA constructs which are capable of being used to replace a defective gene, either in the embryo, or in the children or adults, have been received by Patent Offices. The use of such constructs raises various ethical and safety questions. Such as the possibility that there might be an unforeseen detrimental effect of adding a gene to the genome of a person? The question over whether it is ethical to "play God" and tamper with the genome of a human or a human embryo, with one eye to the public's perception of scientists making a "Frankenstein monster" from this type of research, also needs to be addressed, and could well produce pressure to regulate research into this area.

19. Genetically altered plants are becoming available. These plants have had genes added to or deleted from their genome so that they have commercially desirable properties. Examples include tomatoes which have been altered so that the tomato stays fresh for longer, crop plants which have herbicide resistant genes added to their genome, and potatoes which are able to produce the thermoplastic polyester poly-B-hydroxybutyrate. Such plants again raise issues over the safety of added genes, and whether the gene could potentially find its way into the environment and/or into an undesirable organism.

20. Recombinant bacteria are becoming increasingly important for the production of commercially important enzymes and hormones. Bacteria are also being used to improve the resistance of plants to frost and to control pests such as insects. The use of such bacteria raises safety aspects with regards to unforeseen problems associated with exogenous DNA being added to the bacteria, the prevention of the release of harmful bacteria into the environment, and unforeseen problems associated with the controlled release of bacteria into the environment.

21. Our members in MAFF, on the other hand, point out that while it is possible to postulate "superbugs" and "superweeds" etc none has appeared so far as a result of genetic manipulation and in the case of pathogens it can be argued that a genetically manipulated pathogen is no more dangerous than the pathogen itself. Most of the concern is based on conjecture, and while it is important to be vigilant one can also question whether the controls are too rigorous.

22. Our members in AFRC argue that genetic manipulation is already comprehensively addressed in regulatory terms, but is in need of more basic research input on the movement of genetic material through the biosphere after release.

23. As far as enzyme technology is concerned, the negative issues of operational safety have been dealt with in the detergents sector. For other sectors enzyme technology operates in a non-hazardous physical environment, and its products are highly specific and predictable; all of these factors contrast with the general characteristics of chemically-based food technology.

Q.5 *Should biotechnology be regulated by an industry specific regime?*

24. Biotechnology is not an industry specific capability and should not be regulated on that basis. The use of biotechnology in industry ranges from recombinant DNA technology for the production of therapeutics to fermentation technology for wine, beer and bread production. Biotechnology applies processes and process technology to biological systems and this can be at the level of an individual or a multinational company.

25. A possible exception might be the pharmaceutical industry, where issues of containment are dealt with as part of their core business, irrespective of the use of biotechnologically-derived processes of feed stocks.

26. There are now in place specific regulations which cover geneticaly modified organisms (GMOs), in addition to those which relate to chemical and process industries generally. The recently introduced GMO regulations were heavily criticised in their draft form, but the revised published versions are much improved. These new regulations fall into two groups—Deliberate Release, and Contained Use. The research supported by SERC falls primarily, but not exclusively, into the latter category, and therefore subject only to one set of regulations. This would also be the case for most industrial processes. However, the important are of environmental bioremediation and clean up could require the development of GMOs and their subsequent deliberate release.

Q.6 *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a produce is judged by its characteristics)?*

27. The products of biotechnology must be regulated as products *per se*, within the usage environment at which they are targeted, and their source (eg through which micro-organism, or by which genetic process).

Q.7 *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

28. Our members in AFRC and MAFF claim that this is the only safe approach which will also reassure the consumer. Acceptable risk and particular containment arrangements will vary widely from, say, the medical, industrial chemical (oil, plastics) and food sectors. Thus, the safety of a food product is best assessed by a committee that is expert in novel food products and pharmaceuticals are best assessed by a body expert in pharmacology and drugs. In both cases such expert bodies already exist. However, as far as R&D is concerned it is necessary to maintain horizontal regulation.

Q.8 *How do current regulations compare with those of other competitor countries*

- in Europe
- in the Far East
- the USA?

29. Our AFRC members note that Europe is too diverse to generalise at present. Several countries have only rudimentary legislation in place whereas Germany and Denmark have extremely stringent legislation. The Far East is largely entrepreneurial in approach. Existing regulation is based on existing industrial and commercial activity and very variable in standards, eg well organised in Singapore, but not in Malaysia. The USA is evolving a carefully considered approach based on (a) familiarity and (b) the nature of the product. These are concepts which have guided good risk-based assessment in the past. However, the penalty for getting regulatory processes wrong are very high and public, through the US litigation system.

30. Our Patent Office members illustrate the difference in approaches of the different countries with the example of transgenic animals and the human genome. Transgenic animals are those in which exogenous DNA has been introduced into the cells of an embryo such that the introduced genetic information is present in the cells of the adult. In the case of germline transgenics the introduced DNA is passed onto succeeding generations through the normal reproduction process. Provided appropriate transcriptional control elements have been incorporated, introduced genes may be expressed in the tissues of the transgenic animals. The production of transgenic animals, such as sheep, has a number of commercial applications. They include the production of animals resistant to specific infections or the production of animals with enhanced growth rate, wool quality, or reproductive performance. Sheep capable of producing foreign proteins in their milk, such as hormones which are then easily separated and purified, have also been produced.

31. Whilst bacteria, viruses, and cell lines are patentable, the patentability of whole animals has raised several legal and moral problems. This has come to the public attention in the form of the "Harvard Mouse" or "onco-mouse". The "onco-mouse" is a transgenic organism which has had some foreign DNA inserted into its genome so that it has an increased likelihood of forming tumours. The animals are used to study anti-cancer drugs and treatments. The animal was developed at Harvard University in the United States. Harvard applied for a US patent for the onco-mouse through the US Patent Office, and this was granted in 1988. When they applied to the European Patent Office (EPO) for European Patent under the EPC, the EPO Examining Division threw out the application in July 1989, on the grounds that the EPO did not permit the patenting of animals per se.

32. On appeal in 1990 a Technical Board of Appeal ruled that the EPC excluded only the protection of animals when claimed in the form of an animal variety and did not exclude animals as such. However it was decided that it should be considered whether the invention was contrary to public order and morality. In particular the suffering inflicted on the animals and the possible risks to the environment had to be weighted against the invention's usefulness to humanity. The application was reconsidered in the light of the appeal and granted with effect from 13th May 1992.

33. The decision to grant a patent has led to an outcry among environmental and anti-vivisection groups, especially on the Continent, and has led to a coalition of some 24 animal welfare groups being formed to fight the grant of the patent. Under EPC rules objections may be submitted up to nine months after a patent has been granted. The coalition expects to be joined by other protest groups to fight the patent.

34. The opposition highlights the ambiguity in the EPC "morality clause". Written before the concept of transgenic animals was realised, it gives no helpful guidelines and effectively leaves the question of morality to the Patent Examiners in the EPO. The coalition disagrees with the EPO's interpretation, saying that the engineering of animals designed to suffer is inherently immoral. The objection thrown out at the 1990 appeal to the onco-mouse being a "type or variety of animal" is also likely to be objected to, and to whether patenting life per se is immoral.

35. The growing protest led to a proposed amendment to a European Commission (EC) directive on biotechnology patents to ban animal patents. This was narrowly rejected by the EC Parliament (by a vote of 96–104) in November 1992. Something which appears to be forgotten by opponents is that banning the patenting of transgenic animals will not stop research being undertaken on the animals. A patent only provides a monopoly of an invention, it does not restrict the research taking place. The argument could be

put that the publication of a patent is in itself valuable because it brings the research which is taking place into the public domain and enables a form of monitoring of the research to take place.

36. This issue over the patentability of transgenic animals will need to be resolved. The EPO alone has over 100 applications for transgenic animals pending. With regards to applications under the Patents Act 1977, the Patent Office takes note of the rulings of the EPO, and makes every endeavour to follow them in order to harmonise patents obtained under the Patents Act with those obtained under the EPC.

37. Another emotive issue for some members of the public is the patenting of DNA sequences obtained from humans. A major international project is underway to sequence the Human Genome. The National Institutes of Health in the USA applied for a patent on more than 2000 cDNA sequences with the US Patent Office. This was rejected on 20 August 1992 because many of the sequences had already been published, and once part of sequence had been published, it was considered to be a trivial matter to get a larger sequence or the entire gene. This ruling has been appealed against by NIH.

38. The UK Patent Office also has a similar application from the Medical Research Council filed with the Office. At the time of writing the MRC application has not come to be searched or examined.

39. These applications have raised moral issues over whether it is acceptable for someone to have the patent rights over what is part of every one of us, human DNA. This has again been argued against by environmentalists, again noticeably more abroad than in this country.

Q.9 *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards*

(1) Research

40. Publicly-funded research responds pragmatically to any situation, and the introduction of regulation may merely make the research base broader and investigation more thorough. However, where the funding base remains fixed, or shrinks, less research would be done to underpin the products of biotechnology, in order to accommodate safety/regulation policing research. Regulation slows down direct underpinning research unless more funds are made available, because "licensing fees" will have to be found from the research grant.

(2) Product development

41. Products should have an enhanced image with consumers and a good safety track record should reinforce that image. Failure to regulate thoroughly would inevitably lead to the discrediting of biotechnology as a basis for commercial activity. But regulatory procedures must be applied to home producers and importers alike.

(3) Investment

42. Provided potential investors know what the rules of the game are, they can assess the risks and prospects of return in the long term, so regulation *per se* should not adversely influence an already highly speculative area. The important thing is for regulators to be rational, consistent, and firm.

(4) Location

43. Regulation does have cost implications and the "free for all" economies may attract investment in the short term. There is evidence that some companies are moving to countries with less onerous regulations. This applies particularly to transnational companies. Examples include Bayer AG (Germany) and NOVO Industry (Denmark). However, it is in the nature of biotechnology that it requires careful, detailed policing in the market place both for real safety and perceived safety. If either is undermined, nobody will invest, whatever the location.

(5) Sales and Marketing

44. Regulation can only have a beneficial effect on sales and marketing because it provides the "insurance" for both the marketing people and the customers.

Q.10 *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research in the UK science base?*

45. Not much at the moment because the current regime is relatively liberal, and based on highly developed company responsibility and pragmatism. However, the implementation of the Quayle Report is likely to give researchers/industry in the USA a slight advantage, equally the less stringent interpretation of the EC Directive in Mediterranean countries (Spain, Portugal, Italy, Greece etc) may give them some benefit.

46. Moreover, since the Government trend seems to be to put more of its centrally funded research under market forces, whether internal or external, there will be a tendency, all other aspects being equal, for that research to be conducted in those countries where the legislative framework is most acceptable.

Q. 11 *How best can issues of public acceptance be addressed?*

47. By having visibly sensible and robust regulatory mechanisms to take account of risk and perceived risk, and by applying biotechnology for the benefit of the consumer as well as the producer. Research into methods for "policing" biotechnology is as important as the biotechnology research itself if the UK is to benefit from selling the technology and its products; public acceptance depends on faith in regulation, and the technology depends on public acceptance.

48. Before public acceptance can be obtained, public education must be in place. That education should focus on the fact that the bulk of genetically modified products are not different in kind from "naturally modified" products. It should not hide from discussing perceived hazards. It should be willing to address ethical issues, whether of a religious or secular background. A major focus should be the education of members of the print and electronic media: not soley science journalists, but as wide a range as possible. These form the conduit through which most public fears, concerns and reassurances are promoted. It would be useful if the public could be encouraged to understand the wide area biotechnology encompasses (from beer brewing to laundry to new therapeutics). Also where the use of genetic engineering can be seen to be to human advantage, such as in medicine, then biotechnology, just as much as the medical profession, must receive just recognition.

Q. 12 *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

49. The willingness of UK industry to view the underpinning science base as an integral part of their future business. This may need some pump-priming in the form of tax incentives to aid technology transfer from the public sector, which is an enormous national asset as a source of underpinning science for biotechnology. We hope the committee will visit the HEIs, Institutes and Units to see just how valuable this sector is.

Evidence from Professor Gennaro Marino the Italian Embassy

Thank you for your letter dated 24 February 1993, I am glad to answer your questions as follows:

1. *How important does your Government perceive biotechnology to be?*

Interest in the industrial applications of advanced biotechnologies in Italy dates back to 1985 when a National Committee on Biotechnology was appointed by the Minister of Scientific and Technological Research. A first report was published in 1986 suggesting initiatives to be carried out to foster advanced biotechnology in Italy (see: Ufficio del Ministro per il Coordinamento della ricerca Scientifica e Tecnologica—*Comitato nazionale per le biotecnologie. I Rapporto,* Roma 1986). Following this report two initiatives were launched: (i) a "National Programme on Biotechnology" with the aim of supporting industry for pre-competitive research, with a budget of Lit 209 billion, under the direct responsibility of the Ministry of Scientific and Technological Research (now Ministry for University and Scientific and Technological Research, MURST); (ii) a target project on "Biotechnology and Bio-instrumentations", with a budget of Lit 84 billion, under the responsibility of the National Research Council (CNR) mostly devoted to healthcare with the main goal of strengthening the national network of basic research in this strategic field. Since then, MURST has been the ministry responsible for the policy of advanced biotechnology in Italy, although the Ministry of Industry, the Ministry of Health and the Ministry of Agriculture share part of the responsibility in their own particular sectors. Other major programs launched so far are: the National Program on Bio-electronics (with a budget of Lit 99.7 billion, run by MURST); the CNR targeted project on Advanced Research for Innovation in the Agricultural System (with a budget of Lit 200 billion); the National Program on Development of Advanced Applied Technology in Plants (with a budget of Lit 16.7 billion, run by the Ministry of Agriculture). The private sector has a deep interest in developing the industrial application of modern biotechnologies. The Italian biotechnology companies are associated with Assobiotec which was set up in 1986 within Federchimica, the Italian Federation of Chemical Industries, based in Milan. It is worth recalling that the Italian pharmaceutical industries have a long standing and excellent tradition in the fermentation biotechnologies. Furthermore during the last ten years new small biotechnology companies have been set up. The latter together with established companies give a total figure of 135 biotechnology companies operating in Italy (see C. Spalla, Biotec 6/92, 88–91).

2. *Which developments in biotechnology are thought to raise safety issues?*

At the moment there is no particular concern over safety issues, Nevertheless a "Scientific Committee for Biosafety" (Comitato scientifico per la Biosicurezza) has recently been appointed and is attached to the Presidency of the Council of Ministers (the Italian equivalent of Cabinet Office). At the international level, Italy participates in the OECD Group of National Experts for safety in Biotechnology.

3. *In your country, is biotechnology regulated by a specific regulatory regime?; 4. Do regulations distinguish between contained use and general release?; 7. Has your government implemented EC directives 90/219/EEC and 90/220/EEC. If so, how? If not, when do you expect to do so?*

Two decrees, approved by the Italian Parliament last March, implemented the European Community Directives, 90/219/EEC and 90/220/EEC. Except in some marginal respects, due to national procedures, the content of EEC directives has been fully absorbed into Italian legislation.

5. *Is regulation in your country "horizontal" or "vertical"? Which is preferred by your government?*

The marketing regulations in force in Italy assess the product as to quality, efficacy and safety. Biotechnology products (drugs, diagnostics, enzymes, etc) have so far been authorised to be sold on the Italian market based on these regulations.

6. *Is biotechnology publicly accepted in your country?*

According to "Eurobarometer", the EC biotechnology awareness survey (see Cantley, M, EBIS-European Botechnology Information Service, 4/91, 15–19) 55 per cent of the Italian sample interviewed considered biotechnology "advantageous" and only 9 per cent thought that it would make things worse. Assobiotec believes that, although there are some signs of objections, the prevailing opinion at the level of the government, scientists and media is certainly favourable; however the majority of Italian public is not concerned one way or another and is going to accept biotechnology products as and when they are convenient and/or necessary (see C. Spalla, ed. *II Progresso delle Biotecnologie in Italia,* Brescia, 1990).

It is a pleasure for me to acknowledge the help received by Dr. V. Lungagnani, Projects Co-ordinator of Assobiotec. However, I wish to underline that the above answers do express my personal opinion and do not necessarily represent the views of the Italian Government.

Evidence from the Japan Bioindustry Association

I am writing this letter to you to reply to your enquiry concerning "Regulation of UK biotechnology industry and global competitiveness".

The numbering is taken from your questionnaire.

1. According to the report entitled "Research and Development Plan for Leading and Basic Technology in the Life Sciences" submitted by the Council for Science and Technology and approved by the Prime Minister of Japan in 1984, biotechnology is expected to be a key technology to resolve various problems related to human life such as health care and medicine, environmental conservation, foods, energy and resources.

2. Foods derived by r-DNA technology are likely to raise safety issues, since they go directly into bodies and traditional foods exist as their substitutes.

3. We have several guidelines (not law) for laboratory experiments and industrial application of r-DNA technique by respective ministries and agency.

4. The guidelines distinguish between contained use and field tests of recombinant plants.

5. The present guidelines are composed specifically for r-DNA organisms, but the way of thinking on the product basis is getting popular among relating administrations through the discussion at the expert meeting on bio-safety of OECD. In Japan there are many respective laws regulating products. Products derived from biotechnology shall be regulated by these laws.

6. JBA is not at a position to answer this question from a firm's point of view.

7. The term of biotechnology has a broad range of meaning, but products by cell fusion and cell culture are well accepted by the general public. Acceptance of foods derived by r-DNA technique seems to depend on the benefit of this kind of foods and the understanding by the public.

Should you have any question please feel free to ask me.

Evidence from Dr Julian Kinderlerer, Department of Molecular Biology and Biotechnology, the University of Sheffield

1. *My interest in Biotechnology*

I am a biochemist at Sheffield University who has been a member of the Advisory Committee on Genetic modification since its inception as a committee advising the Health & Safety Executive in 1986. I was a member of the Intentional Introduction sub-committee of ACGM which eventually "became" the Advisory Committee on Releases to the Environment (ACRE). I was also one of the small group of four members of ACRE and ACGM who looked at the responses to both of the consultation papers produced in response to the European Directives and the Environment Protection Act (Part VI) and which have led to the 1992 and 1993 Regulations on both the contained use and release of genetically modified organisms into the environment. I have therefore gained a wide knowledge of the regulatory procedures which have been employed in the United Kingdom and the European Community.

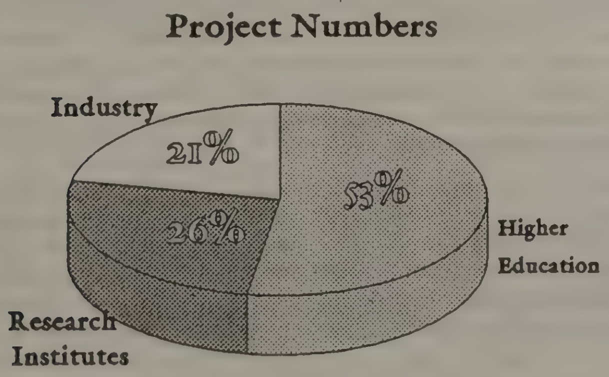
2. *How and why is biotechnology important to UK industry*

Traditional biotechnology, the utilisation of living systems in industrial processes, is possibly the largest industrial sector in the United Kingdom, ranging from sewage disposal to the production of bread and beer. These traditional industries have an enviable record of safe use of organisms in industrial processes. The yeasts used in beer, wine and bread have been used probably for thousands of years, yet there is no evidence of an organism evolving which is pathogenic to humans. Breeding of plants and animals to produce organisms "better" fitted to human needs have also proceeded apace for many centuries, using "traditional" breeding methods.

It is presumed, however, that this question relates to the use of the modern techniques of biotechnology which are the subject of regulation. Using these techniques it is possible both to produce organisms which could not have been manufactured using the traditional methods of sexual crossing, and to introduce novel organisms to the environment in numbers sufficient to ensure a probability of survival greater than might have been had their introduction been a chance event.

The use of recombinant DNA is regulated in the United Kingdom for historical reasons. Scientists originally recommended a moratorium on their own work until the implications of the dangers which might have been associated with the technology were assessed (in July 1974 a National Academy of Sciences working group published a letter in *Science* calling for a moratorium on the use of recombinant DNA experiments). After nearly twenty years of the use of this technology there is no evidence of widespread danger of uncontrolled changes in the properties of modified organisms. The initially strict controls applied to biotechnological experiments have been progressively relaxed as our understanding of the technology has increased. The vast majority of work involving this technology (in terms of numbers of projects) remains in the scientific laboratories of universities and industry which use it to provide information about the systems being studied, rather than for the manufacture of chemicals or for the production of novel organisms.

Genetic modification techniques may be used to provide information about organisms; to provide bulk chemicals in a manner which has not been previously achieved by the insertion of the coding information into organisms which are then used as factories; in the production of fine chemicals in relatively small amounts of chemical compounds difficult and expensive to make using chemical methods (as in the pharmaceutical industry) but under controlled and "safe" conditions because of the use of well-characterised and understood organisms into which new information has been inserted; or to modify organisms which are then released into the environment.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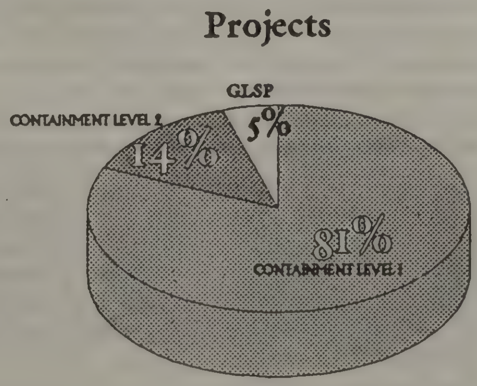
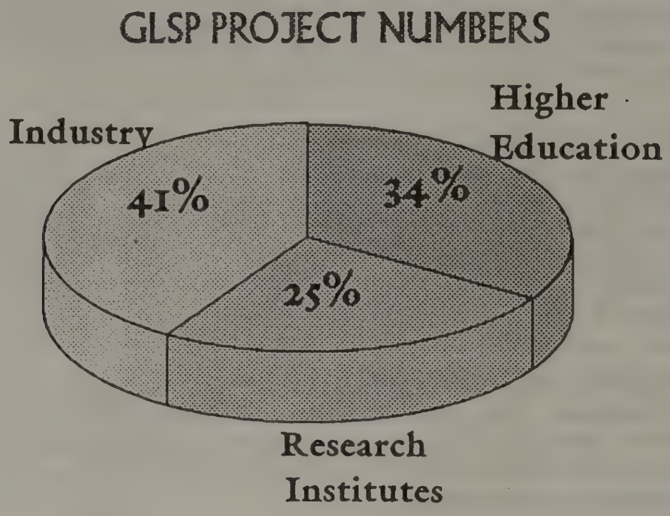

Projects

The overwhelming majority of projects undertaken in 1992 were in containment. Nearly 5,000 projects were notified to the Health & Safety Executive and ACGM, of which 81 per cent were at the lowest level of containment, presumed to be virtually "risk-free" or even "hazard-free". Containment for these projects is limited to good laboratory and microbiological practice as the organisms are disabled and have a history of safe use. About five per cent of the projects were notified as large scale. A very small number of projects (too small to display on the graphs) were performed at higher levels of containment. I have used the information supplied to ACGM abstracted from annual retrospective reports from centres on activities during 1992 to draw the graphs. The number of projects involving the release of organisms into the environment is small, and I believe, likely to remain small relative to the numbers used in containment. Fewer than 80 releases have been sanctioned in the UK since 1986.

These graphs also indicate that the number of projects which involve *Good Large Scale Practice* are relatively small, but their importance may be underestimated as these are the projects which result in the manufacture of chemical and pharmaceutical products; in bulk terms they may dwarf the laboratory scale experiments reported as individual projects. Even then, a large proportion of the projects performed under the conditions of GLSP are performed in laboratories rather than industry:



It seems likely that the major growth in the biotechnology industry will be in the use of benign and well-characterised organisms in controlled and contained systems for the production of both fine chemicals and pharmaceuticals. The difficulties associated with the extraction of these fine chemicals from water based systems on which the organisms grow will be minimised as an understanding of the processes of expression improves. I remain to be convinced that modified organisms intended for release into the environment will be a major industry for many years.

3. *What future prospects and opportunities does the technology offer:*

The technology offers a number of ways in which changes to organisms may be made in order to improve the yield of chemicals required by our society.

It will be possible to introduce genes into well-characterised organisms which may then be used to produce chemicals not easily made using other methods. An increase in the number of copies of a particular gene in an organism or an alteration in the control processes which control the expression (in time or amount) of a particular chemical may increase the yield of that chemical with little or no increase in either the raw materials or energy requirements of the process.

It will be possible to change the chemical constituents of organisms so that their use as food or chemical feedstocks is altered. An example might be a change in the composition of the oil produced by oil bearing seed-crops. The glut of oil-seed rape in Europe would be significantly decreased if the oil composition was changed to resemble that of chocolate, coconut or palm oil. The change of use of the oil produced by this crop would have a huge impact on the economies of the third world, which currently produce these oils, and the use of oils produced by rape would undergo significant change.

The major projected uses of modified organisms intended for release into the environment appears to be the introduction into these organisms of herbicidal resistance or pesticidal properties. If genes coding for enzymes capable of metabolising herbicides are introduced into plants, the plants will be capable of withstanding the use of these herbicides when others are destroyed. If this resistance is stable within the plant and cannot be transferred to other plants which would normally be controlled using herbicide treatment, then there are significant advantages to this procedure. Some argue that less herbicide would have to be used if plants were modified in this way.

The introduction of pesticide into plants may provide plants with resistance to pest attack. The pesticide may be the equivalent of vaccination, providing resistance to viral infection; or may involve the insertion of gene coding for a substance toxic to a pest or fungus which grows on and damages the crop plant. The development of resistance to these toxins by pests may cause problems for the future control pest infestation.

It is possible to introduce the genes coding for all sorts of compounds into crop plants and use these as vehicles for the production of the required chemicals. Little has been done in this area so far, the technology having been used in fermentors with micro-organisms rather than in plants. It will also be possible to modify the techniques used by traditional plant breeders in producing more, and better strains of plants in less time and with less expense (?) than the traditional methods.

Animals have been modified so as to provide better vehicles for laboratory work (for example in testing chemical toxicity or carcinogenicity) and for the production of chemicals. The use of animals is extremely emotive, and may result in a public view of genetic modification which could harm the industry as a whole. In the last few days there have been reports of pigs being produced which contain modifications which allow the transplantation of organs into humans with fewer problems than have been encountered in the past. This will only be acceptable if the public perception of these modifications can be that the organs make the lives of many requiring transplantation much more secure, and that the animals do not suffer (unduly) due to the modifications to their genetic make-up.

The use of gene-therapy for the treatment of disease in humans should not be left out of this discussion. Although not formally part of the biotechnology industry the public perception of the use of biotechnological innovation (particularly in foods) is important to the development of that industry. If gene-therapy is seen as both safe and effective for humans (and perhaps for animals) then the public acceptance of the products of genetically modified organisms will be greater. The Advisory Committees on Genetic Modification and on Releases to the Environment will have a role to play in considering the use of gene therapy in the hospitals. Were a virus particle to be used as the vector for delivery of a gene within a patient, the potential for infection of other humans (some of whom may be immunologically compromised) must be subject to rigorous risk-assessment.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed*

The modification of organisms to produce novel organisms with changed properties represents a risk either to people, particularly those working with or in facilities where the organisms are used in containment, or the environment.

Contained Use:

The risk is probably small, as the assessment of risk indicates the level of containment necessary to contain "problems". I believe that the regulatory framework which is used in the UK, and which has been (albeit reluctantly) accepted by scientists as sensible, makes it likely that those using the technology will assess the risk associated with their use of organisms, and hence use the least hazardous host and vector systems to achieve the required product. An honest assessment of risk, particularly for those procedures performed in containment, will reduce the probability of problems arising from the use of modified organisms to virtually zero. The research laboratory is likely to use organisms and vectors which are most likely to provide the least ambiguous results, rather than that which is most disabled or biologically contained. The assessment of risk is therefore extremely important. Where organisms are being used in an industrial production (or development) the safety of the unskilled workers may be involved in the "plant" is seen as significant, and disabled organisms which are more likely to be biologically contained will tend to be used.

In general, regulation involves the recording of risk assessment, and in some cases prior notification to Government of the intention to attempt a project. Many believe that the regulatory framework is an undue burden on those using the technology. This might be particularly true of those working in research laboratories where the number of different experiments is large, the results unpredictable and therefore the direction of further experimentation unpredictable. This may be solved by the manner in which the regulations have been written, in that projects involving connected programs of work are notified as a single block. This will depend crucially on the interpretation of this regulation.

Release:

Where organisms are released into the environment, the lack of precision in being able to assess the variables that might affect their growth and dispersal decrease the predictive quality of a risk assessment. The introduction of any novel organism into an environment is likely to carry some risk. Changes in host range for a micro-organism or virus may alter the ecological balance resulting in unpredicted events. There are no reliable indicators of the weediness of plants introduced into a new environment. Potatoes resistant to weed-killer may not be a significant problem to those growing potatoes or rapeseed, but are a problem to others who might use the weed-killer as part of their normal production system. That which is a weed to one group of farmers may not be important to others. The introduction of herbicide resistance to potatoes, for example, should not result in the market gardening industry being unable to control the encroachment of weed potatoes into vegetable polts.

Many believe that the introduction of modified species is less unpredictable than that of novel species because the changes introduced into the organism are often well understood and characterised, particularly where the technique involves the deletion or insertion. Of the introductions of plants so far permitted in the UK a significant number have (I understand) not performed quite in the manner expected from laboratory and glass-house experiments, generally in that the plants have been less able to survive in the field or growth room than might have been expected from the changes made to them.

Care must be taken to ensure that the genes introduced into an organism are stable within that organism and cannot normally be transferred directly or indirectly into another organism which would not be subject to the same containment (physical or biological). The risk assessment must take into account the transfer of the gene to other organisms, or the potential for uncontrolled growth which might harm other industries. When using a viral particle as the vector for gene therapy in humans, for example, it will be important to be sure that the transfer of that particle to other (possibly immunologically challenged) individuals within the population cannot cause harm. Appropriate methods of containment can and should be designed which decrease the probability of the transfer of the encoded information to other organisms.

A step-by-step approach to release, with careful analysis of the results of each previous release seems to me to be the best way of addressing problems which are not easily forecast. Scale of release is significant in the assessment of risk to the environment. ACRE in particular has used small-scale as a test for a low probability of harm to the environment.

5. *Should biotechnology be regulated by an industry specific regime?*

6. *Is horizontal regulation better than vertical regulation?*

I am afraid that I cannot see the point of industry-specific regulation of biotechnological innovation except perhaps at the marketing stage, once all the 'hurdles' have been overcome in assessing the risk associated with the new product. The only reason for regulation of the products of genetic modification techniques are the assessment and minimisation of risk associated with the product (which is likely to arise from the method of manufacture) and to assure the community that the products are safe. If the process is contained, then it is the process rather than the product which requires regulation. Clearly appropriate product control will take the process into account in an analysis of risk.

If an organism is released on a pilot-scale or experimental basis, the regulation of that release would have to be based on a wealth of experience gained from all releases, and not associated with a particular type of industry. An organism may be marketed for contained use—as in a diagnostic kit—but it is the deliberate release regulations that apply. The complete list of information for assessment of release which appears in the regulations is clearly not appropriate, nor is it required.

If, however, it is intended to market a modified organism without any form of containment, such as a modified plant variety or a micro-organism which has been modified to act as a pesticide, there will have to be an almost complete lifting of any form of regulation (associated with its modification) as the possibility of recall is remote. Once an organism is cleared for marketing there will have to be a presumption that the only controls that may be applied are those associated with similar, non-modified, organisms or 'chemicals'.

There are risks associated with modified organisms which are not normally expected with other novel organisms, primarily that of the stability of the modification to transfer between organisms. These should have been assessed in laboratory and scale-up procedures which would precede marketing of the modified organism.

Risk assessment is associated with the organism that is to be used. It has to take account the manner of manufacture in order to assess the likely risk, as a modified organism is, by definition, totally novel.

Hence the separation of 'horizontal' and 'vertical' regulation may be artificial. It has always seemed important to members of the committees advising Government that it is the organism that is significant, not the process by which it is produced. The Control of Substances Hazardous to Health Regulations (COSHH) require an assessment of risk for all operations involving work in laboratories and industry. The regulatory framework for the contained use of genetically modified organisms imposes a slightly different regime which in many ways simplifies the manner in which a risk-assessment may be performed for modified organisms.

Historically there are uses of organisms which are not regulated in the same way as processes involving manipulation of organisms. Modification of micro-organisms using techniques other than recombination are not regulated, although risk assessments are required. Most of these techniques are crude and do not provide the same control over the introduced modification as that resulting from recombination. In general, however, material from unrelated organisms is not introduced using these techniques. It has been argued that the changes made using these traditional techniques could have occurred naturally during the millions of years of evolution. That problems from these changes have not been encountered suggests that induced mutational events are not dangerous. The argument ignores two points. Firstly, it is clear that pathogenic organisms have evolved, and secondly, an infinity of time has not yet occurred, and all modifications that might have arisen spontaneously have not yet happened. The argument for not regulating modified organisms because we do not regulate un-modified organisms could be turned over to—why not regulate the traditional processes? The simplest answer is that we do to some extent—the COSHH regulations require an assessment of risk (only to the health and safety of those using the organism) and the introduction of novel organisms to the UK may be covered by the Wildlife and Countryside Act or the Berne Convention. An EC Directive (90/679/EEC) relating to the protection of workers from risks associated with exposure to biological agents at work requires care in the use of all biological agents. I understand that it is the intention of the UK Government to implement this Directive through the COSHH procedures, which do not (of course) consider protection of the environment.

8. *How do current regulations compare with those of other competitor countries*

A regulatory framework for the control of recombinant DNA technology has been in place in many countries since the realisation by scientists of the implications of the technology. There has been a presumption of risk associated with the work. The regulations are in place largely for the protection of those working with the technology, as most of the work is contained. The OECD has been at the forefront of formulation of the framework for regulation, and, therefore, the regulatory regime is similar in most countries. Although the perspective which results in regulation in the EC and the US appear to be different, the controls imposed would not appear to be significantly different in practice. Biotechnological products are evaluated on the risk they pose to human health and to the environment.

The regulatory framework introduced in the UK is, theoretically, the same as that introduced in the other states of the EEC. The interpretation may be somewhat different. This will not matter if a product is to be marketed, as it has to be accepted by the regulatory procedures in all member states. At the experimental stage, however, and particularly when small scale field trials are attempted, the different interpretation of the same framework may be significant. The Community has set up mechanisms through which harmonisation of procedures is attempted. Meetings of the 'competent authorities' may help in harmonising the approach taken by the various member states, and members of the advisory committees and the civil servants attempt to keep up to date with developments in other states through published material, reports of activities and scientific meetings. It may be that the more formal and defined regulatory structure which is being introduced in the Community will be preferred by many companies because of perceived problems with public perception of the technology.

In the United States there are controls at both Federal and State Level. It appears that the contained use of modified organisms (at least in educational establishments) is not regulated, but up to four Federal Authorities may be responsible for release—United States Department of Agriculture (USDA), the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) and the Health and Safety Agency (HSA). The fondness for litigation in the USA means that these agencies are very careful not to overstep the boundaries of the legislation, leaving some gaps in regulation. Some States have their own additional regulatory regime. Where, in the UK all releases of modified organisms are regulated, in the US only genetically modified plants or micro-organisms which contain plant pest sequence or might be plant pests, all microbial pesticides and vaccines fall within the scope of regulation. The EPA is, apparently, considering the issuing of formal rules on the release of micro-organisms other than those mentioned above, and believes that voluntary reporting has occurred in all cases of experimental release of modified organisms.

In practice the apparent differences between the regulatory approaches taken in the EEC and the United States may not be significant. The approach to be taken by the new US Administration to the regulation of biotechnology is not yet known. Although the previous administration indicated a wish to impose as few controls as possible on the industry to ensure its competitiveness in the world market, the approach taken did not (to me) appear substantially different. They both used risk assessment as the basis of evaluation of the risk posed to human health and to the environment. An industrial perspective may be different from mine.

Estimates suggest that the US spends as much as six times more on research and development in biotechnology than does the whole of the European Community. Is it the difference in regulatory regimes which explains the huge difference in spending on research and development of biotechnology? Until recently the methods by which biotechnology were regulated in the different EC countries varied enormously. My perception was that France and Belgium imposed extremely little in the way of controls, whereas it was virtually impossible to perform field trials in Germany. The difference in expenditure amongst the European countries when compared to the USA would suggest that the regulatory process is not a major factor in determining expenditure.

Perhaps the major difference is in the regulation of the contained use of modified organism. We regulate this area of work significantly. It is not regulated in the same way in the United States. This issue is discussed in greater detail below.

9 & 10 *What are the consequences, or likely consequences, of the regulatory regimes on competitiveness of the UK industry, in particular, as regards research, product development, investment, location, sales and marketing.*

It is generally felt that the regulatory regime which had existed in the UK until the changes required by the Community Directives and the Environment Protection Act provided an acceptable framework for the use of modified organisms.

The new regulations, which came into force in February 1993, for the contained use of modified organisms, may have changed the atmosphere for the use of modified organisms markedly. there is a lack of clarity in the definitions of both the types of organisms (I and II) and in the definition of type of work (Type A and B). These are European definitions which were originally designed for the OECD proposals for large scale work and may hinder research when applied to small scale laboratory work.

There has been a great deal of confusion as to Type A and Type B operations. The definition in the regulations of Type A is

> *"any activity involving genetically modified micro-organisms for the purposes of teaching research, development, or for non-industrial or non-commercial purposes on a scale at which the practices and conditions of the operations relative to the culture, volume and numbers of organisms involved is such that—*
>
> *(a) the system used to keep the organism under containment reflects good microbiological practice and good occupational safety and hygiene; and*
>
> *(b) it is possible easily to render the organisms inactive by standard laboratory decontamination techniques.*

This definition **is being interpreted** such that a Type A activity must be for education, research or development, **or** be non-commercial, **or** be non-industrial. If it meets **any** of these criteria, then a question as to the scale of the operation must also be considered. The inverse, which defines a Type B operation, therefore, is that none of the above critera **may be met.** If the process is for research or development and it meets the scale-up criterion, it is a Type A operation. If it is commercial but non-industrial, it is again Type A. A commercial but non-industrial operation will have to be clearly defined in guidance, but it seems that a chemical company which is solely involved in distribution, and not in manufacturing would be engaging in Type A work, where the storage of modified organisms rather than their marketing is being considered. A Type B process is not inherently more dangerous than a type A operation, but it requires consent from the regulatory authorities and is more strictly controlled. That a process done in large quantities involving a workforce that may not be fully conversant with the nature of the organisms being worked will have a significantly greater risk than that done under controlled conditions in a laboratory is not disputed. That type of work requires attention to safety. Commercial and industrial use of modified organisms may not be large scale or conducted in places where non-specialists have access but will still be type B. A small scale research activity is type A, however commercial it is. So a small scale non-industrial activity. Many users (I presume), and all the members of the advisory committees, had not realised until the last few days that the definition of Type B may be interpreted in this way so that it clearly refers to the use of modified organism in a factory environment. Guidance on this issue is crucial, as the delay introduces by inclusion within Type B is very significant.

The classification of organisms into those which are safe, and have been used safely for many years (Group I) and those which are not (Group II) is also a significant change in practice. It is an estimate of hazard rather than risk, where hazard is an intrinsic property that does not take amount or containment into account. Polio viruses could be used safely and without risk on condition they are used in the right form of containment and using the appropriate precautions. An assessment system based on the hazard posed by an organism and which does not take the conditions of use into account brings the assessment scheme into disrepute. A binary scheme which defines most organisms as dangerous and lumps organisms within the same group which are perceived by scientists as being very different in risk potential is again in danger of being "mocked" by scientists who fail to appreciate the difference between hazard and risk. I believe that this new framework may result in less safe working practices and may inhibit research. In theory it is the risk assessment which defines the risk, and which is done first. It has been suggested to me that organism classification is a device used for limited purposes that emerges during the risk assessment but is not the first step or foundation of it. As the classification system determines the requirements for notification and consent it will be that which is first considered by those performing a risk assessment.

As has been demonstrated earlier in this paper, contained use of benign organisms is by far the most important use of modified organisms. It is feared that this new framework could be rigorously interpreted which would result in a significant paperwork and financial burden on research laboratories which is not justified and which may eventually lead to corners being cut and a greater degree of risk associated with procedures than the practice which had developed in the UK over many years. The United States does not appear to regulate the contained use of modified organisms in anything like the same way, if at all.

The advice given by ACGM to civil servants was that the new regulations should, so far as was possible, impose a similar burden on research and development under containment as has been the practice for the last few years. The major change should have been that an environmental assessment is now required. If, as may be the case, the regulatory burden is significantly increased (and a wait of up to 3 months before work may commence is imposed), then UK & EC research and industry will be harmed. Many UK companies are likely to fund research and development in laboratories where the work can be conducted quickly and with the minimum of regulation.

The guidance provided by ACGM to those using organisms in containment will be crucial for they will define both the manner in which the regulations are likely to be interpreted by the Health & Safety Inspectorate and other Government agencies, but also provide the framework for producing risk assessments which may assist scientists in their understanding of the requirements.

The public information requirements of the new legislation may also be significant at the research level. The results of the work, and hence the likelihood of patentability, may not be known at the research level. European Patent law is (apparently) significantly different to that in the United States, and the prior disclosure rules may conflict with these public information requirements because of the difficulty in prediction what might or might not become important when starting the research. This raises severe problems, for I believe that the public disclosure provisions are the best mechanism for improving the public perception of biotechnology. The regulations have attempted to address this issue. During the consultative phase before the regulations were made those concerned at too much information being made publicly available, and those concerned that too much information would be withheld were brought together to attempt a reconciliation. I understand that some of the environmental groups are concerned at the quality of the information being placed on the register, and have written to the Department of the Environment of their concerns.

It is at the research and initial development level that we have most to fear from the regulatory requirements insofar as they affect the competitiveness of UK and EEC industry. In the US research and development releases of micro-organisms are exempt from legal requirements for regulation, but releasers are encouraged to inform the appropriate Authorities, and the EPA believes that they have been informed of all releases which fall under the toxic substances control legislation. the position in the US is far from clear, with the new Administration considering change.

Once the process proceeds to product testing and marketing, however, I believe that the stricter regulatory framework may work to the advantage of European industry, for it may form a protective cloak and assist in overcoming consumer resistance to products formulated using recombinant technology. A major difference, however, is that the US currently does not charge applicants for consents (or notifications of use) for release of modified organisms.

The economic support for biotechnological innovation in the USA is much more likely in the transfer of research and researchers than any regulatory regime. As research and researchers concentrate in the United States, this drift will accelerate. This provides a serious problem for Europe which will have to be addressed. The comparative strength of British and European in the sciences could be at risk from the greater overall expenditure on research and development observed in the USA.

11. *How best can issues of public acceptance be addressed?*

I believe that public information and the knowledge of a reasoned and reasonable regulatory framework for the use of modified organisms may be the most useful way in which to gain public acceptance. The media have a tradition of finding the sensational, and can sensationalise the technology in ways which make the public fear the introduction of new technology. This happened in 1991 when a television program, Chimera, was exploited to suggest the ways in which the technology could be abused. The Daily Star of the 9 July 1991, for example, carried a front page headline 'A monster is born, and its going on in real life too!', referring to genetic modification. In the centre page spread they stated 'In bizarre laboratory experiments, genetic boffins have already—implanted human sperm in female chimpanzees ... pure cross-breeds of men and apes;—created 12 ft giant mutant pigs. . .;—planned to create cows the size of elephants and breed chickens without wings. The "article" continues "Stephen Gallagher, who wrote Chimera after researching the horrors of genetic engineering, says 'Scientists are in a furious race to create a species of powerful sub humans'". Public information about that which is actually happening, and an openness about the experiments being done will allay public fears more than anything else.

The public will also be reassured if a regulatory framework exists which ensures that experiments are not being done without people outside a particular laboratory knowing about them, and that an independent review of the risk assessment has been made. The safety committees which are required for contained use, and which involve members with expertise without the particular laboratory, are the best guarantors of safety.

Julian Kinderlerer

25 March 1993

Evidence from Professor M D Lilly (University College London)

The term "biotechnology industry" while convenient is not really appropriate. Like many other technologies, biotechnology has an input into many different industrial sectors, in particular pharmaceuticals, food and drink, chemicals and waste treatment.

Responses to questions

1. I am Professor of Biochemical Engineering at University College London, a Director of The International Institute of Biotechnology, and a member of the Biotechnology Joint Advisory Board (BJAB). I was a co-author of the OECD Report on biotechnology in 1982.

2. Three of the strongest sectors of the UK manufacturing industry are pharmaceuticals, chemicals and food/drink. They are already dependent upon both scientific and engineering advances in biotechnology and will be increasingly so to remain competitive. The proportion of the chemical industry using biotechnology is rising rapidly.

3. The range of potential new products is vast, ranging from foodstuffs, through pharmaceuticals and healthcare products, to fine and bulk chemicals. By 1990 six therapeutic proteins made by recombinant DNA technology each had annual sales of more than $ 100 million. The number of such products is increasing each year. It is estimated that sales of biotechnology-derived products (excluding fermented foods and drinks) will

be between 26 and 41 billion ECU by the year 2000. European industry faces intense competition, principally from the US and Japan but also South-East Asia, and its share of the world market will depend on the timely introduction of new products at a competitive price.

The recent guidelines issued by the US and FDA indicating that new products should be single enantiomers rather than racemic mixtures will put more emphasis on biological routes making use of the reaction specificity and stereospecificity of enzymes.

rDNA technology will make a further important contribution by enhancing the synthesis of enzymes both for the manufacture of products by fermentation, such as antibiotics, and for use in reactions to introduce stereospecificity into chemical molecules.

4. There is public concern about the use of genetic manipulation, despite its proven benefits. More generally, there is perceived risk by the public of the use of food additives which outweights the greater actual risks from microbial contamination of foods. This highlights the need for a better understanding by the public.

5. All products resulting from biological processing should be regulated on the basis of safety, efficacy and quality. In some cases the criteria used may be sector specific. There are many common features and operations in the biological industries which should be covered by overall regulations.

6. It is vital that regulation should be vertical if innovative processing developments are not to be stifled. However, at present in the food industry it is sometimes difficult to define a product and regulation must be on the process.

7. There are certain pharmaceutical products, such as those classified as biologists, where horizontal regulation is applied but, as analytical methods improve, there should be an evolution to vertical regulation.

8. The UK has always had a good reputation for its approach to regulations, such as those on genetic manipulation, avoiding the adverse situation which has arisen in some other European countries as a result of strong pressure groups.

9. It is essential that the regulatory regime is no more onerous than required to satisfy the criteria in (5) above and that burearocracy is kept to the mimimum. Many large companies in the UK are multinational and will shift their activities to the more favourable location if regulation becomes too burdensome.

10. There is concern that the CEN standards for biotechnology being drawn up may be overprescriptive and based on subjective judgements. It is essential that good biochemical engineering studies be carried out to provide the numerical data on which standards can be properly based.

11. Public acceptance of biotechnology has not been helped over the last decade by the attitudes and statements of some governments, academics and industrial companies. As a result it has a very negative image as far as the public and media are concerned. The public are not aware of, or do not understand, the benefits that have already resulted from biotechnology. Many organisations, including BJAB, are addressing this issue. It is part of a broader problem—the need to make the public more able to assess the risks involved in all facets of their lives.

The biological industries have an exceptional record on safety but it will be foolhardy to convince the public that there is not and never will be an element of risk.

12. For UK industries using biological processing to remain competitive it is vital that new and improved processes should be developed in the shortest time possible and be safe, reliable, economic and environmentally acceptable.

Universities have a vital role to play in achieving these industrial objectives by

(i) undertaking biochemical engineering research on the fundamental principles underpinning the design, development and operation of bioprocesses,

(ii) providing the trained biochemical engineers needed by industry.

Collaboration between academia and industrialists in the biological industries is good and has been fostered by schemes, such as LINK.

It is important that Government Departments and Research Councils ensure that they have a co-ordinated long-term policy for support of biotechnology. I believe that BJAB will make an increasingly important contribution.

Evidence from Jose MacDonald

I find the emphasis on industry and global competitiveness in biotechnology rather worrying. Whilst realising that this technology has many benefits to offer in many spheres of our lives, it is essential that we also realise that this technology could present a Frankenstein situation in the wrong hands or if marketed without adequate standards and amounts of research.

This technology is still in the experimental stage and the true extent of its effects on the ecology, particularly animals and man, is not yet fully understood. Such knowledge I realise would take many years, and it is customary to go ahead with new products and rely on further information becoming evident during marketing.

Unlike chemical products, biotechnological products can spread within species and across species in some instances. Their characteristics may be inheritable. It may not be possible to withdraw them when detrimental effects become obvious.

It is vital therefore that greater caution is exercised when marketing biotechnological products than with previous classes of products. Sprays etc may have produced effects not originally realised and these may effect a whole generation. Biotechnological effects could effect several future generations and therefore have longer lasting and more serious effects. They require longer research programmes and wider coverage.

In order to prevent the enthusiasm of commercial science from developing research into a profit orientated exercise, with true deductive reasoning and unbiased evaluation being sacrificed, it is vital that non-industrial, independant research is encouraged. This would involve greater government expenditure on academic and independant research, enabling freer debate between scientists and more exchange of information at the fundamental stage.

1. My interest in biotechnology commenced with the introduction of promotion of r BST by the chemical companies, at a time when milk quotas were being introduced. To use artificial growth hormones to increase a product that was about to be rationed did not appear logical. I therefore researched deeply into this product and became involved in campaigning against it.

My experience as a farmer in animal husbandry, as a consumer and as a grandmother worried about the conditions under which my grandchildren will be living after my demise, led to me taking the development of some biotechnological products very seriously.

Some of the standards prevailing, which I became aware of, caused me to be extremely cautious regarding the propaganda emanating from the relevant companies, regarding the genetically engineered product, recombinant bovine growth hormone. I have discussed it with members of The Veterinary Products Committee, the senior Ministry Biotechnologist, members of the European Parliament and Commission as well as members of world-wide organisations opposed to the licensing of this product. My past experience as a Rural Education Officer in West Africa under Colonial Office, led me to feel great concern over the way in which this technology is being promoted in the third world countries as well as in Europe and the US.

2. This technology is important to UK industry just as all industry is important to our economic success. It would be gratifying if we could lead the world on biotechnological development. If we could set the right standards of research and assessment.

3. This technology offers possibilities of tackling disease and inherited faults in animal and man more successfully. It offers the use of genetic engineering for improved crop varieties and the use of it for pest and disease control.

4. All developments in biotechnology raise issues of safety. These issues need to be thoroughly addressed through exhaustive, unbiased research. Freedom of information between scientists and consumers would help to evaluate possible detrimental effects and, if possible remedy them. Section 118 of The Medicines Act denies such possibilities in its present form. It needs to be revoked.

The issue of licensing r BST has presented most of the dangers involved in present licensing procedures and has, unfortunately exposed the power of the multi-national companies' ability to spend large amounts on promotion and propaganda of a product, prior to completion of assessment. This product has been promoted world-wide to farmers as an elixir of improved milk production increase. The detrimental effects have not been made known, in fact they have been kept very secretive from the people who would be expected to buy this product. Research has been biased and detrimental effects ignored by excessive use of the word "insignificant" in protocols, where the percentages of cases showing undesirable effects might seem small in the laboratory but would involve great loss on the farm.

Inadequate research on this project regarding safety to humans is a vital issue. The VPC and Ministry biotechnologist have given us assurances of safety to consumers continuously drinking treated milk. These assurances are merely verbal and not substantiated by an accurate research whatsoever.

I have taken legal advice as to the definition of a medicine under the Medicines Act of 1968. Whilst it includes a therapeutic effect, which most people would demand, it also includes the ability to alter the anatomy and/of physiology of a living creature to increase or decrease production.

Morally this offers a philosophy equivalent to that of the Nazi scientists.

UNDER LEGISLATION WHICH DEMANDS SAFETY, QUALITY AND EFFICACY AS THE CRITERIA FOR LICENSING, BUT NOT ETHICS, BIOTECHNOLOGICAL PRODUCTS COULD BE MARKETED UNDER VERY DANGEROUS SITUATIONS.

Results of work on genetically engineered plants shows some transfer of implanted character to plants some distance away. Although only a small percentage are affected this number would be considerable after several years cropping and would escalate. This could create problems with resistant weeds, plants resistant to sprays and susceptibility to fungal diseases and pests.

Genetic development of higher yielding varieties tends to reduce immunity to problems normally found in normal conditions. The hardiness of varieties is of serious concern as it frequently seems to be sacrificed eg the resistance to drought of tropical engineered crops. The reduced resistance to stem borer in genetically engineered varieties of rice is of importance.

5. The above evidence makes clear my opinion that biotechnology would be a dangerous technology if regulated by an industry specific regime. Money is a necessary evil but, when it takes priority over safety to living creatures it is a key to catastrophe.

8. Current regulations in Europe are more rigid and cautious than in the Far East. The far eastern countries, especially Japan are more concerned with commercialising genetic discovery than safety.

The USA has a more open system of assessment, not tied to an official secrets Act as in this country. It is however corrupt. I have unearthed instances of commercial bribery and even commercial influence in the FDA and in some Senates when licensing procedures are discussed. Emoluments such as free overseas holidays and other 'carrots' have been offered as reward for promotion of product license decisions, even in Britain. This situation actually became recognised on a BBC programme. Whilst accepted as normal standards in the commercial world they would not be accepted in government occupations. There is therefore a discrepancy between standards of integrity in industrial biotechnological matters and those of government standards.

This needs to be addressed if biotech. research is to be considered reliable and safe.

9. The proper control of the regulatory regime is likely to slow down the process of licensing in this country. However if ethics and safety issues are to be treated seriously there is no alternative. Eventually it would lead to greater respect for products produced in this country and eventually greater investment. Open discussion and less secrecy would expose any shortcomings in the regulatory procedures in other countries and so would operate in favour of the U.K. If locations are affected by controls on environmental pollution etc this also would operate eventually in our favour. Increased overseas respect for our standards would affect our sales and marketing.

10. This is answered by the previous statement.

11. Public acceptance can be obtained by encouraging trust. The public suspect secrecy and lack of open discussion and this applies to biotechnology as to other spheres. If it is obvious that the investigations on safety and other criteria are thorough, unbiased and honest then the public will trust the products.

Too many detrimental effects on the recipient or environment resulting from biotech. products will damage the market. The standard and independence of research conclusions is therefore vital. More thorough investigation and time involved needs to be taken with biotechnological protocols, in view of the more widespread effects involved, and to avoid too many undesirable effects emanating after marketing.

12. I believe that the definition of a medicine, and many of biotechnologies products will be defined as such, should be therapeutic. Genetically engineered products must not be used for product yield enhancement at the expense of the environment or the comfort of living creatures.

The U.K. biotechnology industry has got to be seen as having nothing to hide, as unbiased in its research and directed towards producing products for enhancement of the quality of life for living creatures. To use expensive propaganda, economy of truth and biased research to further profit at the expense of therapy will eventually affect public awareness and be detrimental to commercial competitiveness.

Jose MacDonald.

Evidence from the Medical Research Council

1. *What is your interest in biotechnology?*

Definition: In framing this reply we use the following definition of biotechnology: "the industrial application of biological organisms, systems or processes" (Cmnd 8177). These applications are very diverse and it is hence misleading to think in terms of a single biotechnology industry.

MRC interest: As a Research Council, the MRC's interest lies in the advancement of knowledge and the generation of concepts and methods so that they can be developed and applied, bearing in mind the interests of both the taxpayer and industry, to the benefit of human health. The MRC consequently needs a strong and effective health-care industry—with a strong biotechnology base—to ensure that its research findings result in improved health-care products. In that the knowledge and methods are often generic they may also be relevant to other fields of benefit to the UK economy, eg chemicals, agriculture and instrumentation.

2. *How and why is biotechnology important to UK industry?*

Successful exploitation of new biological understanding will be the basis of extensive future industrial activity. Many established industrial sectors will need to embrace biotechnology in order to maintain a competitive edge. Biotechnology also offers the prospect of new company formation both in existing areas and in new industrial sectors, building on the application of knowledge of biological processes (see the response to Question 3 below). The UK has a high standing internationally in biological research with the potential that this brings for new wealth-creating industries.

3. *What future prospects and opportunities does the technology offer?*

Prospects and opportunities have been much enhanced by the development of recombinant DNA technology (genetic engineering) together with a host of other advances in structural, molecular and cell biology which are leading to rapid growth in the knowledge of the genomes of organisms, of the products of the genes and the roles they play in cells. This has already led to the production of human growth hormone and insulin and to diagnostic tests for genetic disorders. But now there is also the possibility of the rational design of specifically altered organisms, cells or molecules, tailored to the functional needs, in place of the random changes that occur naturally. Examples include the development of humanised antibodies with the potential for the treatment of a range of diseases including lymphoma and somatic-cell gene therapy for the treatment of genetic disease and cancer.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

From an MRC perspective, the relevant biotechnologies that raise the most serious safety issues concern therapeutic agents. In part these are analogous to concerns about conventional drugs (whether synthetic or natural products) in terms of toxic side-effects; the major extra dimension comes from concerns about the possibility of replication and release (eg early concerns about infection by the organism *Escbericbia cali* used for the production of engineered molecules and recent concerns about vectors to be used for somatic gene therapy). It should not be forgotten that the introduction of *non-engineered* organisms into new environments also carries potential risks as well as benefits.

Safety concerns were raised and addressed by scientists themselves when recombinant DNA technology was first mooted and have been ever since.

5. *Should biotechnology be regulated by an industry specific regime?*

No. As we have commented above, it is misleading to think in terms of a single biotechnology industry. Biotechnology should be regarded as a powerful discipline which can be used to create a competitive edge in a wide range of distinct industries related to health care (therapeutics, vaccines, diagnostics), agriculture and food, environmental remediation etc. As regulation is broadly based on assessment of risk/benefit relationships for society and for individuals, different regulatory regimes will be needed for different industrial sectors.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

Vertical regulation, based on objective analysis of the risk/benefit relationship to both individuals and society, would in our view be more appropriate. Regulation at the level of process cannot distinguish between constructive and harmful applications.

8. *How do current regulation compare with those of other competitor countries?*

- *in Europe?*
- *in the Far East?*
- *the USA?*

The MRC has no special knowledge in this area but it is likely that restrictions in some other European countries (eg Germany) on research in genetics may have had an adverse impact on industrial R&D investment.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards*

(1) *research*
(2) *product development*
(3) *investment*
(4) *location*
(5) *sales and marketing?*

The competitive edge of any industrial sector will inevitably depend on the regulatory regime. There is much to be learned in this general area from the systems for the regulation of new drugs. Regulation should be open and objective and take place at a minimum number of appropriately timed stages, adapted to different circumstances. The situation that currently applies to somatic gene therapy work should be avoided; at present such work may need to be addressed by a new Department of Health Committee, the Committee on Safety of Medicines, the Health and Safety Executive, the Committee on the Release of Genetic Modified Organisms and a Local Research Ethics Committee.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

See 12 below.

11. *How best can issues of public acceptance be addressed?*

Public acceptance of biotechnology remains at a low level (though the position may well be better in the UK than in some other countries) mainly because the public is unsufficiently aware of its benefits. We believe that the public would be far more inclined to accept biotechnology if more effort were put into explaining exactly how it affects their everyday lives. This ties in with the MRC's belief that it is the understanding of value of science in society which is important, rather than of the scientific process for its own sake.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

The lack of clarity of the regulatory process in the UK/EC may affect the exploitation of biotechnology in the UK. There are also other more important factors which currently constrain explotation. For much new biology, exploitation will require creation of new companies. This has taken place on a massive scale in the US and created extensive new employment opportunities and economic activity. For a variety of reasons (eg unwillingness to invest in high risk but high return R&D, lack of tax incentives to support R&D, lack of suitable "exit routes" for investors, lack of entrepreneur scientists) exploitation is constrained in the UK.

There is also a need for a reform of European patent law. US-based inventors currently have an advantage because in the US the law allows patent filing within the 12 month period following publication. Action is needed to achieve international harmonisation in the patent field.

Evidence from MEDTAP EUROPE (John Hutton Esq)

Thank you for your letter of 19 February inviting me to submit written evidence to the Select Committee on *Regulation of the UK Biotechnology Industry and Global Competitiveness.* Although the Medical Technology Assessment and Policy Centre (MEDTAP) of Battelle has expertise in the area of medical technology and its economic evaluation, we do not have detailed knowledge of the current regulatory system for biotechnology products in the UK or other countries. As a consequence, we cannot supply answers to the specific questions in which evidence is invited.

However, we do feel able to comment on Question 12 regarding other factors influencing the competitiveness of the UK biotechnology industry. A major focus of our research has been the pharmaceutical industry which is a major developer and marketer of biotechnology products. The pharmaceutical industry is heavily regulated and it is by no means clear that shifting from horizontal to vertical regulation would significantly decrease the regulatory burden on new drugs developed through biotechnology.

In determining how to reform the regulatory framework for biotechnology, it is important to understand the entire regulatory context for biotechnology products. It is well-known that the regulatory framework for pharmaceuticals, whose purpose is to ensure product safety, imposes severe costs on the industry. It is estimated that the cost of bringing a new drug to market is approximately $259 million (in 1990 US dollars). A large proportion of this expenditure is due to the extensive testing in the development stage after discovery, particularly the required Phase II and Phase III clinical trials. Although regulation of biotechnology at the discovery stage may impose some additional costs on pharmaceutical products developed this way, the bulk of the costs are likely to be due to regulation in the development phase.

There may be a case for reducing the regulatory burden in the development phase for products developed through biotechnology. For example, if genetic engineering is used to create a natural hormone such as insulin, does it need to undergo the same type of testing as a new chemical entity? In the case of genetically engineered human insulin, it would appear that much of the regulatory framework could be simplified. It appears that it may be necessary to rethink the regulatory framework for controlling new pharmaceuticals in the face of the innovations from genetic engineering.

A second issue is whether the regulatory framework should remain so heavily concentrated before drug introduction with so little regulation after the drug is introduced. Clinical trials will never be sufficient to understand the effectiveness of a new therapy because of small sample sizes, restrictive inclusion criteria, and restricted definition of the drug's clinical indication. To understand the real effects of the new therapies requires their use in actual practice. This suggests that in the future much more of the regulatory emphasis should be moved to Phase IV after the drug is released. If more information was collected during the Phase IV period, development costs for new drugs could be reduced, and the process of evaluation could become a function of the health care system.

What the above discussion suggests is that in the case of pharmaceuticals, the real issue of regulation is in the developing phase. Although there may be some marginal improvements by decreasing the regulatory burden in the discovery phase, it is unlikely that horizontal regulation of biotechnology is a major barrier to competitiveness in the UK pharmaceutical sector. From the governments' perspective it may be inefficient to decentralise regulation to multiple departments, because then each department would have to develop its own expertise in regulating biotechnology. The question is whether the regulations need to be the same for all of the applications of biotechnology? It is possible to relax the regulations for different types of products without moving to a completely vertical mode of regulation for all products.

It is important to realise that the major factor influencing the success of the pharmaceutical industry is the policy of the healthcare system with regard to drug licensing and re-imbursement. Current healthcare reforms in the United States and Europe are oriented towards cost containment, and one of key areas targeted for control is the fast growing drug budget. There is a strong likelihood that healthcare reforms will lead to downward pressure on prices in the pharmaceutical sector and limitations on which drugs are reimbursed. Battelle MEDTAP is currently undertaking a study of the impact of healthcare reforms on the rate of innovation in the pharmaceutical industry. As a major developer of and customer for biotechnology, the financial health of the pharmaceutical sector will be a key factor determining the success of firms active in biotechnology. The report should be prepared in the early summer. If it would be of interest, I would be happy to send you a copy.

Thank you for giving me the opportunity to contribute to the work of the Select Committee, although I fear that on this occasion Battelle MEDTAP has little to offer you on your principal concerns. However, we would welcome the opportunity to contribute to any future studies which you might undertake in the areas of healthcare policy, industrial policy, and medical technology.

Supplementary evidence from the Ministry of Agriculture, Fisheries and Food (MAFF)

EXECUTIVE SUMMARY

There are several methods of producing transgenic plants. The choice of technique is determined, in the main, by the taxonomic group of the target crop.

For the majority of non-graminaceous crops, Agrobacterium and protoplast based techniques successfully produce transgenic plants. Cereals and some legumes, however, do not respond well to these methods but there has been some success with the "biolistic" method.

TECHNIQUES TO GENETICALLY MODIFY PLANTS

1. The following methods have been used with varying degrees of success to produce genetically modified plants.

Agrobacterium tumefaciens

2. Agrobacterium tumefaciens—mediated gene transfer by infection of tissue explants has been used extensively in the production of transgenic crop plants. The vast majority of these are dicotyledonous species. In agrobacterium-mediated transformations the transgenic-DNA is inserted and integrated into cells at a wound site. In species with a wound response these cells divide and can be used to generate transgenic plants. However, some economically and nutritionally important crops, such as cereals and certain legumes are extremely difficult to transform by this method. In these plants, wounded cells accumulate phenols and die and therefore any transformed cells do not proliferate.

Agrobacterium rhizogenes

3. This bacterium has been successfully used to transform a variety of dicotyledons and gymnosperms to give "hairy root" cultures. These cultures have been used to regenerate transgenic plants. Similar restrictions on the range of transgenic plants that can be produced by A.tumefaciens also apply to A.rhizogenes.

Viral Vectors

4. Plant viruses with DNA genomes have been modified to carry foreign DNA. Infected plants can express the genes introduced by the viral vector. In general however, viral DNA is not integrated into the plant genome and viruses are excluded from floral meristems preventing seed transmission. It consequently seems that the use of viral vectors will concentrate on transient gene expression studies rather than the production of stable transformed plants.

Direct gene transfer to protoplasts

5. Several methods are used to introduce DNA into protoplasts, which are plant cells from which the cell wall has been removed. These methods include

- electroporation
- treatment with polyethylene glycol

- sonication
- fusion with liposomes
- co-cultivation with A.tumefaciens

Whichever method is used, the recovery of stable transgenic plants is dependent on regeneration from protoplasts. A wide variety of transgenic plants derived from protoplasts have been produced with herbaceous dicotyledons predominating. Cereals and some legumes are difficult to regenerate from protoplasts.

Biolistics

6. "Biolistics" involves the use of a particle gun which bombards the plant tissue with tiny ball bearings carrying the genes to be inserted into the plant. This method is of great potential use as any tissue, including chloroplasts and pollen, can be used as a target. Species that are difficult to transform with Agrobacterium or regenerate from protoplasts can be transformed by this method.

Liposomes

7. There have been some investigations to see whether liposomes can transfer DNA to intact cells and tissues. So far there has only been limited success and the future of this approach to produce transgenic plants is unclear.

Incubation of cells and tissues in DNA solutions

8. Several attempts have been made to transform tissues by incubating them in DNA solutions. Doubts have been expressed as to whether this process could produce stable transgenic plants as a matter of routine. The use of electroporation techniques in solutions has also proved of limited value. The use of a microlaser to burn holes in cell walls with a UV laser and then incubating these cells in DNA solution has met with limited success, although it has been suggested that the technique may be of use in chloroplast transformation.

Microinjection

9. This technique requires the use of a powerful microscope as the DNA is injected into the nucleus of individual plant cells by micro-pipettes. Great skill is required to manipulate the individual plant cells on this fine scale.

Macroinjection

10. This technique involves the injection of DNA into plant tissues but only transient gene expression has been observed. A limited number of experiments have been undertaken using this method and the uncertain results suggest that the long term future of this technique is not clear.

Pollen tube pathway/Pollen transformation

11. DNA solution has been applied to the cut ends of rice pistils. The resulting seedlings were claimed to be transgenic, but these claims have been questioned by other researchers. So far, attempts at pollen transformation have met with little success.

Evidence from Napier University, Edinburgh (Professor M Wright and Professor C F A Bryce)

EXECUTIVE SUMMARY

- There has been a shift from research and development to application and production.
- Future prospects and opportunities are likely to take place in a series of waves (Kondratieff Cycles).
- Acute recruitment problems exist in specific areas.
- Continuing interaction between academia and industry should be facilitated.
- Education and training should be broad based and incorporate ancillary skills.
- There is a need for harmonisation of qualifications and the duration of training periods.
- Consumer acceptance is crucial to biotechnology's contiuing development and must be improved.
- Consumer resistance can encumber commercial prospects.

Biotechnology offers major opportunities for social and economic benefit through the large industrial sectors of healthcare, agriculture, food and drink and environmental protection. However, if UK biotechnology is to participate in this undoubtedly inevitable worldwide development it is crucial that it maintains its competitive position with Europe, the USA and Japan so that the UK does not again become an importer of products and technology.

The two principal areas of interest in biotechnology at Napier University are the provision of high quality courses at Diploma, Degree, Honours Degree and Higher Degree levels and the execution of pure and applied research in selective topics within biotechnology. Particular areas of ancillary interest include studies on the manpower and training needs for biotechnology in Europe (in collaboration with the CEC), curriculum development in schools and institutions of higher education in the third world (in collaboration with the ICSU Committee on Science and Technology in Developing Countries) and in developed countries (in collaboration with the British Council). Other non-specified issues are covered largely through active committee membership on the British Coordinating Committee for Biotechnology (BCCB), the European Federation of Biotechnology (EFB) Working Party on Education, the EFB Task Group on Public Perceptions in Biotechnology and the UK Interest Group on Education in Biotechnology.

The number of employees in new biotechnology companies has increased from two- to ten-fold according to country in the period 1982–88. There has been an accelerating shift in emphasis from research and development to application and production which is likely to continue. Biotechnology has an industrial impact **directly** by creating new companies (many of which are proving very successful despite the current recession) and **indirectly** through investment and equipment and service suppliers, and through its applications in healthcare, agriculture, food and drink *etc.*

The future prospects and opportunities offered by biotechnology are likely to take place in three successive waves (Kondratieff Cycles):

1. diagnostic, pharmaceutical and animal health products
2. agriculture, animal husbandry, speciality chemicals and environmental control
3. cheaper products, commodity chemicals, mineral leaching and electronics.

Successful application depends on what is possible, what is realisable and what is wanted, while consumer acceptance is crucial to biotechnology's continuing development.

Acute recruitment problems presently exist in areas such as protein biochemistry, downstream processing, product purification, microbial physiology and bioinformatics while there appears to be a sufficiency of genetic engineers. In general there is a shortfall in technicians. The three main areas of concern at present are:

1. the very significant decrease in the number of graduates proceeding to postgraduate and postdoctoral training
2. the major movement for training from southern European countries to the north due to the lack of facilities in the former
3. the variation between European countries in the training period for the PhD degree which inhibits mobility

Biotechnology is multidisciplinary and, while larger companies tend to favour specialist training and smaller ones more generalist, all personnel must be able to communicate, to work effectively in such a context and be trained accordingly. The continuing development on the interaction between academia and industry should be facilitated by all possible means. Industry involvement with course design and course content should be encouraged and, in particular, with postgraduate courses which benefit greatly from being designed and taught in collaboration with industry. Undergraduate degree courses should be broadly based with specialisms being taught only in the final stages.

Resources and facilities in academic institutions for training should be improved in general and especially in regard to postgraduate training. Urgent measures need to be taken in relation to the current decline in the numbers of graduates proceeding to postgraduate and subsequently postdoctoral training, especially in the already existing shortage areas such as protein biochemistry, downstream processing, product purification, microbial physiology and bioinformatics.

Personnel trained in biotechnology must be able to operate as part of a multidisciplinary team. For this reason they should have training elements in management, marketing, and financial and legal aspects including intellectual property rights, as well as a sound basis in science and technology which itself must inculcate multidisciplinary competence and attitudes. The exchange of good practice, resource materials and learning programmes for students and staff throughout Europe should be facilitated and encouraged. The provision of short courses on a range of topics should be developed for updating and retraining of staff. Training grants for permanent staff are required to help improve mobility. There is a general need for harmonisation of qualifications throughout Europe and a particular need for the harmonisation of the PhD training period.

Reports such as those of the European Commission to the Council of Ministers and European Parliament, the Commission of the European Communities' Eurobarometer Survey and of the UK Advisory Council on Science and Technology have pointed out that consumer resistance and fears for safety can seriously encumber commercial prospects and that it is imperative therefore that problems of public acceptability be recognised and responded to. It is of crucial importance that the general public's understanding of biotechnology be encouraged and increased. This can only be achieved by sustained effort by all involved with biotechnology and by using as effectively as possible all appropriate means (Consensus Conferences in central Europe are proving to be particularly effective in this regard). A considerable effort is now being expended to determine and positively modify the public perception of biotechnology. This requires carefully targeted educational material to decouple the topic of biotechnology from issues such as eugenics, animal welfare, *in vitro* fertilisation *etc*. Fortunately, at present this is being addressed on a number of fronts and in a variety of media formats, using good practice established from like concerns in relation to the nuclear energy industry.

With regard to safety, which clearly has to be monitored and assured, then a number of steps are already in place through UK legislation and/or European guidelines and directives. These would appear to be overly complex, open to misinterpretation and to incorporate a significant element of safety which will be reassuring to the general public initially although it may be that this can be relaxed over a period of time. Clearly, the most contentious issues at present are the release of genetically-modified organisms (GMO's) into the environment and the possibility of "patenting life". The UK is less well advanced in the experience and the legislation for this activity as compared with some of our fellow EC countries. Part of the current changes in biotechnology result from the widespread changes in the political climate. The European infrastructure in science is poorly developed at present compared with the USA and Japan largely because there are twelve separate national science policies among EC member states, notwithstanding EFTA and COMECON countries. As the European Single Market continues to develop, borders will disappear and be replaced by transnational networks. A close monitoring of the effects of the release of GMO's into the environment will be of interest and use to all, in a global sense.

The fine detail of the associated and current legislation is best known by the industries operating in the field whilst our own experience in this aspect of the work of the Sub-Committee of the Select Committee is very limited with respect to the detailed specifics of the legislation and, consequently, we shall omit making a response in this area.

Professor M Wright, Vice Principal

Professor C F A Bryce, Dean of Faculty

Evidence from the National Consumer Council

SUMMARY AND CONCLUSIONS

1. Consumers are becoming increasingly interested in the foods they eat and especially the processes through which foods are taken before they reach our tables. The innovation in the field of biotechnology and the implications for foods are the latest developments to face consumers and possibly the most complex to understand. Consumers are, by nature, wary of new processes that will affect the every day foods they eat.

2. The National Consumer Council's interest in biotechnology is in:

- ensuring that an adequate and appropriate system of regulation is in place which will reassure consumers that novel foods have been assessed for safety; and
- ensuring that consumers are informed and educated about these new developments so that they are enabled to make informed purchasing decisions.

3. Apart from issues of safety and information, the innovations in the field of genetic modification raise other ethical concerns which the NCC believes must be addressed. Such concerns could emerge as one of the most important aspects of the battle for public acceptance.

4. The National Consumer Council calls for an independent committee of representatives of intersted bodies to be set up whose remit would to consider the ethical questions of biotechnological developments in food from the consumer point of view.

5. Whilst consumers recognise that no amount of data can ever conclusively 'prove' the total safety of any products or processes, consumers buying new foods must be confident that the safety assessment procedure is rigorous and transparent.

6. The NCC welcomes moves in the proposals for an EC Regulation on Novel Foods and Ingredients to require the prior evaluation and approval of all novel foods. We also believe that the move away from the 'twin-track' approach, as outlined in the latest Presidency proposals, and towards a system of Member States' approval with Commission authorisation could be a step towards meeting our calls for greater clarity and transparency.

7. The type of information and the way it is presented is a key to consumers' reaction to a new product. Biotechnology is claimed to have to power to improve the environment, the animals and plants used in agriculture, our health and the quality of the food we eat. But there is still a vast gulf between scientists' and industry's knowledge and understanding on the one hand and consumers' on the other. At present (according to a 1991 Eurobarometer survey), people place more confidence in consumer and environmental groups as sources of reliable information on biotechnology than they do in public authorities. With more openness and dialogue between government, industry and consumers, greater understanding and trust could be established.

8. We very much support the steps taken by the Food Advisory Committee in its attempts to give consumers information through labels about genetically modified products. They have recognised the

essential role of information (in this case, labelling) in upholding the principle of consumer choice. While the NCC recognises that the complexity of the technology itself makes it difficult to categorise for labelling purposes, we believe that consumers should be enabled to make informed purchasing decisions.

9. Labelling cannot be the whole story. There is a need for proper information so that consumers can form a balanced view and take independent decisions about the consequences and benefits of such technology. That cannot be transmitted on a label alone. There must be a much wider information campaign which addresses consumers' genuine concerns.

10. Tha gap between scientific knowledge and public perception can be very wide indeed. It may be the former which drives the industry but it will be the latter which determined its success.

1. *The consumer interest in biotechnology*

Consumers are becoming increasingly interested in the foods they eat and especially the processes through which foods are taken before they reach our tables. We want to go back beyond the farm gate and understand how our foods evolve. The innovations in the field of biotechnology and the implications for foods are the latest developments to face consumers and possibly the most complex to understand.

The National Consumer Council (NCC) recognises the importance of supporting such technical and scientific innovations and the increased choices these could offer consumers. Indeed, in the field of medicine, the part played by biotechnology will greatly enhance our lives and is appreciated by consumers.

How the results of biotechnology fit into the food chain, however, is a different matter. Consumers are, by nature, wary of new processes that will affect the every day foods they eat. The NCC's interest in biotechnology, therefore, is:

- to ensure than an adequate and appropriate system of regulation is in place which will reassure consumers that novel foods have been assessed for safety; and
- to ensure that consumers are informed and educated about these new developments so that they are enabled to make informed purchasing decisions.

2. *Consumers' attitudes to biotechnology*

Compared to the vast resources invested in technical research and product development, little attention has been paid to investigating consumers' views on biotechnology. The existing evidence suggests that consumer acceptance cannot be guaranteed.

In the Spring of 1991, a Eurobarometer survey by the European Commission (1), which interviewed 12,800 people, included a number of questions on biotechnology. The results showed that public understanding of it was very low: only one in five respondents claimed to feel capable of answering the questions (although these was more awareness about it in the northern European countries than in the southern).

Only 50 per cent of people thought that biotechnology would improve our way of life over the next twenty years. This was the second lowest score—telecommunications (80 per cent), solar energy (76 per cent), computers (74 per cent) and new materials (63 per cent) were all regarded as more useful.

There was more acceptance for research involving plants (77 per cent) and micro-organisms (86 per cent) than that involving animals (47 per cent) and people thought there were greater risks attached to work with transgenic animals than with plants and micro-organisms. There was consensus about the need for 'government control', with over 90 per cent in favour of control of all research involving genetic modification.

Medical and environmental applications of biotechnology were more likely to be considered worthwhile (96 per cent and 97 per cent respectively). Only 65 per cent agreed that food applications could be useful: the potential risks were seen to be higher.

A second consumer survey, this one focusing on the factors influencing consumer acceptance of biotechnology specifically in foodstuffs was carried out in 1990 by the Institute for Consumer Research (SWOKA) in the Netherlands. (2) There was a generally low level of acceptance for the use of "genetic engineering" (their words)—with an average rating of 5.6 on a scale of 38 points. There was little variation in individual reactions to different food products; respondents who rated the acceptance of one product low, or high, tended to rate others similarly.

Consumers' socio-economic status, religion and age made very little difference. Those with a more technological outlook appeared to show greater acceptance of the use of genetic engineering in food production, although those who already knew something about genetic engineering showed lower levels of acceptance.

Attitudes were influenced by the *type* of genetic engineering involved and the *purpose* of the end-product. For example, its use in the reduction of pesticides or for health purposes were more acceptable than for improving the taste or prolonging the shelf life of food.

The amount and type of information available about genetic engineering influenced the level of acceptance. Where foods were presented as new, but with no reference to genetic engineering, they were rated positively;

if it was revealed that they had been using genetic engineering, the acceptance level was lower. If a possible adverse effect was mentioned, the products were rated negatively.

These studies suggest that consumers' concerns about the new technologies, especially in the market for food, have to be addressed if the developments are not to be unilaterally dismissed by the very people who could ensure their success.

3. *Is it ethical*

Consumers are concerned about safety of any new products and their ability to make informed choices about such foods. But the innovations in the field of genetic modification raise other concerns which the NCC believes must also be addressed. The Eurobarometer survey quoted above found that 20 per cent of respondents thought that genetic modification of animals, for example, was, on moral grounds, totally unacceptable, while a further 28 per cent felt it should be considered on a case-by-case basis. We believe that ethical concerns about genetic modification could emerge as one of the most important aspects of the battle for public acceptance.

These include concerns that:

- genetic manipulation involves "playing God" by tinkering with the stuff of life;
- genetic manipulation assumes a "reductionist" view of life encouraging us to adopt the chemist's perspective and look upon all forms of life as "just DNA";
- genetic manipulation breaches barriers and boundaries between species which "nature" has set up through the process of evolution to prevent genetic interactions between species. Or that GM programmes breach the "creationist" view that all existing species were created once and for all by God and that to attempt to modify this arrangement constitutes a form of blasphemy. Both perspectives see species as "sacred" and genetic manipulation as a violation of this "sacredness";
- genetic manipulation distorts mankind's relationship with the rest of nature. By engineering plants and animals for our own purposes, we come to assume that we own other life forms;
- genetic manipulation of animals involves "unnatural" experiments and can cause suffering. And if human genes are transferred to animals, what human attributes, potentialities and rights go with them;
- genetic maniputlation could represent the first step on a slippery slope that leads inexorably to a nighmare programme of universal "eugenics".(3)

These ethical concerns need to be openly debated. The European Commission's group of advisers on bio-ethics is an important step forward and could play a significant part in this process. In setting up the group, the Commission has at least recognised the need for greater dialogue. The actual influence of the group remains to be seen. But it could make a useful input into the new authorisation procedures set out in the proposed EC regulation on novel foods and ingredients, in addition to bringing the whole ethical debate on genetic modification into sharper focus.

The NCC is concerned, however, that it will remain remote from consumers. How will its members know what the concerns and anxieties of consumers are? Will they discuss issues openly and will members be encouraged to seek views from different groups at national level? The need to encourage a better informed dialogue suggests that ways should be found to increase consumer representatives' involvement in the important decisions that are being taken on our behalf.

Our book, *Your Food: Whose Choice?* (4) called for the setting up of an "independent committee of representatives of interested bodies whose remit would be to consider the ethical questions of biotechnological developments in food from the consumer point of view". As the book went to press, the Ministry of Agriculture, Fisheries and Food announced the appointment of an independent, expert group to report on ethical concerns which might arise from the consumption of foods derived from genetic modification programmes.

The National Consumer Council welcomed the setting up of this group and submitted a paper outlining some of the important consumer questions. (5) We concluded that a significant number of people are concerned enough (for whatever reasons) to want to know whether their foods have been genetically modified. They need to be able to give voice to those views and to have confidence that they will be taken seriously.

One way forward is to look (as responses to the Netherlands survey quoted above have already suggested) at each development on case-by-case basis and for the new ethics committee (as called for by NCC) to decide on the ethical/moral issues surrounding each one.

If consumers had confidence in the membership of such a committee, felt that they have had ready access to it and that they were being consulted about, and therefore influencing, decisions, the issues then become ones of safety and choice.

4. *Safety*

Consumers must be satisfied that any new product or process is safe. This is particularly true for food. New technologies like irradiation and biotechnology are still little understood by the public and are perceived as potentially dangerous.

The novel foods assessment procedure in Britain, which identifies the type and number of safety tests and the information required for different applications, ought to reassure consumers of the rigour of the system. We believe that the Advisory Committee on Novel Foods and Processes and its decision-tree approach to safety and risk assessment has much to commend it and in recent responses to the proposal on a EC Regulation on Novel Foods and Ingredients, the NCC has argued for the adoption of such a procedure across the community. (6)

There is a need to harmonise the notification and authorisation procedures for all products coming onto the EC market. The 1992 proposals would have put responsibility for deciding whether a new product contains novel ingredients or has been processed in a novel way on the company intending to market it. If the food or ingredient was classified as novel, according to the criteria set in the draft regulations, the company would be obliged to carry out a scientific assessment of it.

A two-tier system was then proposed—with products assessed either at the national or the European level. A list of "experts" would have been drawn up by the Commission to be responsible for assessing the safety data on a new product or process. Some such products would only require approval by at least one of the official "experts" and subsequent notification to the Commission before being placed on the market. Other products considered to present a greater risk would have to undergo a more complex, centrally-operated Community authorisation procedure before being placed on the market.

These were welcome developments. Prior evaluation and approval of all novel foods, based on mandatory safety assessments, is long overdue. One of the main weaknesses of the 1992 proposals, however, was that they relied too heavily on the opinion of only one expert at the initial stages. We were strongly of the opinion that for consumers to have confidence in the decisions being taken on their behalf, properly structured committees made up of independent experts representing different disciplines and including consumer representatives should be established at Member State level. These committees could be structured along the lines of the UK Advisory Committee on Novel Foods and Processes. The establishment of common criteria to guide the work of these committees would be essential.

The current Presidency proposals (7) are to move away from the "twin-track" approach and for applications for authorisation to place a novel food on the market to be submitted to the "competent authority" in the relevant Member State. "Favourable opinions" would then be forwarded to the Commission for final authorisation.

These proposals seem much more likely to meet our demands for transparency and clarity although we shall consider in further detail the criteria proposed as the role of the commission and the Scientific Committee for Food.

5. *Information*

The NCC was disappointed that those 1992 proposals did not make clear provision for labelling and information. As every marketing manager knows, the type of information and the way it is presented is a key to the consumer's reaction to a new product. Biotechnology is claimed to have the power to improve the environment, the animals and plants used in agriculture, our health and the quality of the food we eat. Those involved in the research and marketing of its products have a great interest in its success; only time will tell whether their claims can be substantiated.

Meanwhile, it is important that the debate is opened up to the public—the consumers of the end-product. There is still a vast gulf between scientists' and industry's knowledge and understanding on the one hand and consumers' on the other. According to the Eurobarometer survey in 1991, the media is the public's main source of information about novel foods and biotechnology. Technical reports use scientific language and jargon incomprehensible to non-specialists. At present (according to a 1991 Eurobarometer survey), people place more confidence in consumer and environmental groups as sources of reliable information on biotechnology than they do in public authorities. With more openness and dialogue between government, industry *and* consumers, greater understanding and trust could be established.

The decision-making processes in many areas of UK government policy have traditionally been secretive. For example, the government's food and other advisory committees of independent experts have been completely closed to the public. There are improvements, however. Consumer representatives have been appointed to the Food Advisory Committee since it was set up in 1983 and, more recently, to the Advisory Committee on Novel Foods and Processes. Although the papers discussed at meetings remain confidential, agendas, notes of the meetings and annual reports are now published. These improvements are welcome. But there is a need for even greater openness if consumers are to be in a postion to influence the direction of development and have confidence in the process.

The other side of the coin is that of information on food labels and elsewhere. Do consumers have enough information to make informed purchasing decisions and is this information clear, accurate, useable and not misleading? If the answer appears to be "no", those consumers will start asking "what are they doing to our food?" or "are they trying to hide something from us?"

We very much welcome the steps taken by the Food Advisory Committee in its attempts to give consumers information about genetically modified products. We recognise the problems that they face. The complexity of the technology itself makes it difficult to categorise for labelling purposes. How far back in the food chain should labelling apply? Is it possible (and acceptable) to label some forms of modification and not others? As more and more foods are produced using this technology, it may become impossible to distinguish between those which have and those which have not.

The Food Advisory Committee's guidelines are a step forward in that they recognise the essential role of information in upholding the principle of consumer choice and recognise the need for some form of labelling.

Clearly, labelling cannot be the whole story. There will be a need for proper information so that consumers can form a balanced view and take independent decisions about the consequences and benefits of such technology. That cannot possibly be transmitted on a label alone. There must be a much wider information campaign, which addresses consumers' genuine concerns, if "products of gene technology" are not to suffer the same public rejection as irradiated products.

6. *Conclusion*

The gap between scientific knowledge and public perception can be very wide indeed. It may be the former which drives the industry but it will be the latter which determines its success.

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Evidence from the National Farmer's Union of England & Wales

The NFU welcomes the opportunity to comment on some aspects of the development of biotechnology in the UK.

The NFU's interest in biotechnology arises from its role in representing the great majority of farmers in England and Wales. Biotechnology could have a dramatic affect on the competitiveness of British farmers and growers, on the structure of the industry, on its methods of production and on its ability to develop new markets for its produce.

We consider that biotechnology in agriculture can best be considered as a series of techniques which give access to a wider gene pool and permit faster and more accurate progress in producing desired microbial, plant and animal genotypes. We do not foresee biotechnology replacing conventional plant and animal breeding but rather working with them.

Biotechnology potentially offers a vast range of prospects and opportunities in agriculture. It offers ways of altering agriculture's output to satisfy more closely market demand. New products could be developed, for instance there could be longer shelf life fruit and vegetables. New uses could include production of pharmaceuticals, other chemicals and biofuels. Biotechnology could provide ways of improving the efficiency of production, better protection against competitors, vaccines and unfavourable conditions, and better diagnostic tests for quality control. It could also lead to the creation of crop and livestock types with useful agronomic traits, for instance disease resistance.

In the past improved plant and animal breeding has made a very significant contribution to the development of UK agriculture and its enhanced efficiency and competitiveness. Biotechnology has the potential to increase this rate of change. Its impact could vary between commodities and between different areas of production, whether within the UK, the EC or the world as a whole.

In short, the NFU would expect a significant and growing impact of biotechnology on the agronomic practices of farmers and growers and the economics of farming and on agricultural policy formation.

The development of biotechnology, just as the development of any new enterprise, will inevitably raise interest in issues of safety and ethics. Safety of the user, protection of the environment and of public health all must be assured just as they would for any new method of producing food. The first way in which safety issues must be addressed is through work designed to provide an objective basis on which to assess risk. This is clearly a matter for close Government involvement in co-operation with informed opinion, science base, public interest groups and those companies developing the use of biotechnology. The persistence of genetically modified organisms in the environment and their ability to cross-breed with naturally occurring relatives needs to be thoroughly discussed and understood.

Safety procedures in biotechnology need to pay proper regard to the concerns of the public. These concerns will be at their greatest when genetically modified products appear in the food chain. Studies of both short and long-term food safety will be an essential element in the determination of regulatory controls. Farmers, as prime food producers, are very sensitive to consumers' fears and prejudices in this area.

The NFU is deeply concerned that the regulatory approach should ensure consumer acceptability of biotechnology as well as user, environmental and consumer safety. At this stage we believe that horizontal regulation, covering the use of biotechnology and the release of genetically modified organisms, is desirable to ensure that both these targets are achieved.

We are not aware of the details of regulation of biotechnology in other parts of the world. Our preference would be for widespread international agreement on regulation, firstly to ensure the greatest degree of safety but secondly to ensure that there is no competitive distortion between the agricultures of different countries. In practice it may well be best to concentrate on securing more uniform EC arrangements. Indeed, we welcome the EC's proposed novel foods directive, although we believe it requires some modification.

Differences in regulatory arrangements in different countries could result in the biotechnology industry concentrating its efforts in those areas with the weakest controls. Successful plant and animal breeding programmes are a significant factor in maintaining a competitive UK agriculture. UK farmers and growers could therefore be placed at a significant competitive disadvantage. If we are not involved at the cutting edge of developments we will be left behind.

As already indicated, the NFU views public acceptability and understanding to be a vital component in securing the successful uptake of biotechnology by farmers and growers. Lack of public acceptability would damage farmers' interests if public fears and worries over even the limited use of biotechnology for a product led to marketing difficulties for similar products which did not rely on biotechnology.

The NFU believes that the most thorough debate on the use of biotechnology is necessary. Scientists and commercial developers of biotechnology should realise the importance of presenting their research findings in ways which allow the public to understand and respond to developments. They should also ensure that the public understands the safety precautions they take in their research programmes. Every effort should be made to inform potential users, such as farmers and growers, as well as the general public.

The Government should consult widely and be open on the basis of its decision making. It should develop an open regulatory approach and ensure that the regulators are clearly separate from the industry and its commercial pressures. We welcome the Reverend Polkinghorne's expert group which is looking at genetic modification and food issues but the debate must go much wider.

Safety and regulation must play the major role in determining the uptake of biotechnology in the UK. They could also affect the competitiveness of the UK biotechnology industry. The other major factor affecting competitiveness is the ownership and protection of biotechnological developments.

Many of the products of biotechnology will be animals and plants which could be used for breeding on farms. The NFU is conscious that the developers of genetically modified animals and plants need to make an economic return on their investment, but farmers traditionally breed their animals without payment to any holders of rights. Even in the plant sector, where plant breeders' rights are a long-established feature, farmers and growers are able to use the seed obtained from their own cultivation of material which is subject to a plant breeders' right for their own purposes—"farmers' privilege". The NFU believes that these positions should not be disturbed.

Despite the obvious difficulties, the competitiveness of the UK biotechnology industry will be safeguarded best by the development of at least an EC-wide, and preferably worldwide, rules governing intellectual property rights in genetically modified animals and plants.

Evidence from National Office of Animal Health Ltd. (Roger Cooke Esq, Director)

Thank you for sending us a copy of your press notice on this subject.

NOAH represents the manufacturers of animal medicines in the UK, our 34 member companies are responsible for approximately 96 per cent of the UK's £210 million turnover in animal medicines plus a similar volume of exports. This is a highly international industry and many of our member companies operate throughout the world. The products covered are diverse, ranging from the simplest remedies sold in pet shops, through materials used by farmers to protect the health of their animals, to the most sophisticated products used by the veterinary surgeon. In response to the specific points in your press notice:

1. *What is our interest in biotechnology?*

Veterinary medicine, like human medicine, operates at the cutting edge of life science technology. The use of biotechnology to advance the progress of animal medicines to prevent and relieve animal suffering and improve productivity has been under consideration by veterinary pharmaceutical companies throughout the world for many years. Biotechnology is, in particular, seen as the way forward for the production of the next generation of animal vaccines, such as vaccines for the pig disease "Aujeszkys" which have recently been licensed in the UK and Europe. The use biotechnology as a means of replicating naturally produced substances such as insulin and the growth hormones bovine somatotropin (BST) and porcine somatotropin (PST) is already well advanced. BST is already used in many parts of the world and has recently been approved by the Medicines Commission in the UK and the Committee on Veterinary Medicinal Products in Brussels as meeting the necessary requirements for licensing. As you may be aware, a political moratorium on the use of BST is currently preventing the granting of licences for BST and its use by dairy farmers in the European Community.

2. *Why is biotechnology important to the UK industry?*

As outlined above the industry sees biotechnology, with its opportunities for producing natural substances (previously only available by extraction from cadavers) on a commercial scale and the production of safer, cheaper and more effective vaccines for disease control, as providing the next generation of products.

Vaccination is seen as the long term trend in animal medicine as a preferable alternative to chemical treatment. Vaccines based on gene technology offer the prospect of preventing many diseases, including those caused by internal parasites in a simple and cost effective way.

3. *What future prospects and opportunities does the technology offer?*

Following on from the above points, biotechnology offers the opportunity to prevent diseases which currently can only be treated by chemical intervention. The advantages of vaccination are:

(a) long term protection from one or two doses;

(b) prevention of disease without the need to resort to chemical control;

(c) improved animal welfare by preventing rather than treating disease.

The ability to prevent disease, rather than requiring animals to become infected and suffer before treatment, alson means that performance is maintained at the most efficient level, thus adding to the prosperity of farmers.

4. *Safety Issues*

In animal medicine, biotechnology can be used in two ways.

(a) Firstly, as with the production of insulin or BST, the technique is simply a step in the production process leading to the production of chemicals. In this type of production there is no risk from genetically modified organisms reaching the environment. It can be argued that the end product is no different from one which might have been produced by sophisticated chemical manufacturing techniques; in this context issues of safety relate to the final product rather than to the utilisation of biotechnology during the production process.

(b) Secondly, the production of vaccines. Here organisms are modified by gene technology to produce vaccines which could not be manufactured by conventional techniques. It is worth noting that vaccines produced by biotechnology are likely to be safer than those produced by conventional methods. For example, a live organism rendered harmless by a known alteration to its genetic makeup can be monitored much more easily in the field, and is likely to be much more stable than an organism where the mechanism of attenuation is unknown and not clearly 'visible' in tests. Similarly a sub-unit vaccine produced by biotechnology is likely to pose less of a problem than a whole inactivated organism.

In both systems it is our view that the existing, highly stringent and exhaustive system of safety testing and scrutiny for animal medicines, as required by British and European medicines law, means that any safety issues are already well covered and in our view no additional protection is needed.

5. *Should biotechnology be regulated by an industry specific regime?*

No—biotechnology is a technique which is applicable to many different industries. In our view the concern about biotechnology whilst understandable in such a new science, is nonetheless greater than the situation warrants, and ignores the many benefits which biotechnology will bring to companies and consumers alike. Most high technology industries which are likely to utilise biotechnology are already well regulated and, certainly in the case of the animal medicine industry, existing regulatory systems are more than adequate to deal with the issues involved.

6. *Horizontal or vertical regulation?*

Following on from 5, we believe that horizontal regulation is inappropriate. Vertical regulation, aimed at monitoring the production processes and the final product, is already well established for the animal medicine industry. The concept of horizontal regulation for biotechnology would be analogous to requiring horizontal regulation of a particular technique such as "electronics" whatever industry happened to be utilising the technology. This is not done for other areas of technology and we do not believe it is appropriate for biotechnology.

7. *Should regulation evolve from horizontal or vertical?*

The points outlined above indicate that we *do not* believe that horizontal regulation is appropriate. There is already European regulation to control release of 'genetically modified organisms'; this is all that is required.

8. *Current regulations around the world*

British law on biotechnology is already closely linked to European law and based on European Directives. However, there are fears that the British tendency to show excessive zeal in implementing and enforcing European legislation could extend to biotechnology the damage which has already been done to other parts of British industry. There is a general need for British officialdom to be more aware of the attitudes to implementation and enforcement which exist in other member states. We fully support the Government's drive for de-regulation but do have doubts as to whether the culture of British officialdom will actually allow this initiative to achieve results.

We have no direct experience of regulations in the Far East or USA. We do understand that in some parts of the United States, notably California, pressure group activity is adding to the difficulties of biotech industries along similar lines to those experienced in northern Europe (see 11). The situation in the Far East, which could be characterised as being in a "pre-regulatory" era, means that technological advance is likely to proceed far quicker in that region with potential damage to the competitiveness of the emerging biotechnology industry in the UK and Europe. Indeed the pursuit of biotechnology in countries lacking the appropriate level of control (as we believe is already in place in GB) will either lead to the strangulation of this developing science or its completely unregulated development and neither scenario is to the ultimate benefit of the public. It is notable that, due to the pressures in Germany (see 11), in particular, German owned companies have chosen to base their biotechnology activities in other parts of the world which might be regarded as more "hospitable".

9. *The consequences of the regulatory regime?*

We are not aware of specific problems relating to biotechnology. We have pointed out, above, the overall regulatory attitude of British officialdom; the animal medicine industry can cite many examples of products that have not been allowed to reach, or remain, on the British market even though they are available in other parts of the European Community, even though the same European Directives nominally apply.

10. *See above.*

11. *Public acceptability*

In a number of parts of European political pressures based, not on science but on concerns over a selective interpretation of "ethics" and wholly inaccurate and in some cases wilfully misleading information, have already done considerable damage to the development of European biotechnology, particularly in northern European countries such as Germany. In the UK we are fortunate that this particular problem has not developed to any serious extent.

It is unfortunate that the activities of negative pressure groups and sensationalist journalists have allowed a negative attitude to biotechnology to emerge. In general these may be characterised as fears of the "Frankenstein" syndrome. We believe that these concerns must be addressed and in particular would suggest:

(a) greater openness and "transparency" of the regulatory system. We have already suggested, for example, that consumer and industry observers should sit on the UK regulatory committee for veterinary medicines (the Veterinary Products Committee) as already happens in France; and in the EC's "Committee on Veterinary Medicinal Products".

(b) greater publicity on the positive benefits resulting from biotechnology and gene technology. In our own industry the example of the ability to produce effective, safe vaccines and, on a very topical note, the development of a treatment for cystic fibrosis in humans–both demonstrate the very real value of biotechnology;

(c) by pointing out that for many industrial uses biotechnology is only a step in the production chain and the final product is no more than another "substance" which happens to have been produced by a sophisticated technique.

12. *Factors affecting competitiveness of the UK industry*

As already addressed, the main problems are public attitudes and the general over-regulatory culture of British officialdom. A further point is the question of the protection of intellectual property both through the patent system and the drive for greater openness and public access to licensing data. For animal medicines, biotechnology suffers from the same problems as other animal medicine developments in that very long development times, and delays in licensing, mean that a considerable proportion of patent life has already been lost before the product arrives on the market. Biotechnology offers extreme examples of this and it should be pointed our that, for example, BST has been under development (in the USA) since the late 1970's but has not yet achieved a licence in Europe. It is quite easy to predict that the entire patent life of this product could have elapsed before it is finally allowed on to the European market. Changes to patent law which allow patent time to start from the point of licensing rather than from initial registration of the patent will be of considerable benefit and enable companies who make enormous investments in the development of biotechnology products to recover those investments through sales. The debate over the patenting of life forms is particularly pertinent here.

As mentioned above, we support the general idea of increased transparency as a way of improving public confidence in the regulatory system, however, this needs to be balanced by proper checks to ensure that data, produced at great expense, is protected when supplied to the authorities in support of a licence application. Early drafts of the private members "Medicines Information Bill" could have done considerable damage to industrial property and driven research and licensing of pharmaceuticals out of the UK. Fortunately, considerable improvements in the safeguards offered to industry have emerged as amendments during the Committee stage of the Bill. Nevertheless, it does emphasise the conflicting pressures on the industry and the need for legislators to be aware of the damage that could be done by naive acquiesence to populist pressures for freedom of information.

I hope you find the above comments of assistance, we are aware that a number of companies represented in this industry have already been called to give evidence to the Committee. NOAH would be very pleased to meet with the Committee to give further background to the above comments, given sufficient notice.

Evidence from the National Rivers Authority

1. The National Rivers Authority (NRA) is a non-departmental public body with broad responsibilities for the management on inland and coastal waters of England and Wales. This includes responsibility for control over the discharges of wastes into such waters, either directly by the issuing of consents under the Water Resources Act 1991, or indirectly by setting limits for discharges from certain prescribed industrial processes, which then provide minimum standards for authorisations set by Her Majesty's Inspectorate of Pollution under the Environmental Protection Act 1990. Within this general pollution control framework the NRA therefore has an interest in biotechnology for two specific reasons:

- it has to consent the discharges of wastes arising from processes that use them; and
- it has to monitor discharges of wastes from essentially any potential source, for which methods using biotechnology are increasingly being deployed.

The NRA also has a general duty with respect to conservation of the aquatic environment. It therefore has an interest in the potential impact of any genetically engineered organisms on other aquatic fauna and flora.

2. It appears to be the case that the continual pressure being placed upon dischargers to reduce the polluting potential of their discharges—not least as the result of pressure being brought to bear by both the NRA and HMIP through recent legislation—is leading to a change of practice away from the "end of pipe" solutions to waste control and more towards waste minimisation, and treatment at source. This has, in turn, led increasingly to the development of specially designed waste treatment processes to remove specific pollutants at source. Many of these use modified biological systems.

3. The EC Urban Waste Water Treatment Directive (91/271/EEC) may require the removal of nitrogen, phosphorus, or both, from certain sewage treatment works' effluents which discharge into areas identified as "sensitive" for the purposes of the Directive. Conventional chemical treatment has generally been used in the past by dischargers to remove these materials, but this involves an additional stage of treatment. Specific modification of the biological stage of the sewage treatment process to remove nitrogen and phosphorus is now available, including the use of biological aerated filters and fluidised beds to remove nitrogen, and modified bacterial populations to remove phosphorus. For industrial effluents, anaerobic digestion using mixtures of bacteria are also now more widely used. A common feature of many of these new plants is the ability, through automatic computerised control systems, to manage plants in such a way as to be able to overcome the former constraints on treatment caused by unexpected changes to inflow volumes or compositions, thus ensuring that biological treatment can be used more confidently with regard to meeting regulatory standards. The development of such technology is to be encouraged.

4. Where such processes involve the use of specifically enhanced bacterial populations, there is nevertheless some concern of the effect these may have if released. The release of Genetically Modified Organisms (GMOs) is of course specifically controlled via Part VI of the Environmental Protection Act 1990: they are also the subject of two EC Directives—90/219/EEC on their contained use, and 90/220/EEC on their deliberate release. There are potential uses of GMOs as tracers of pollutants—for example the use of modified

bacteriophages–but their future development is likely to be very dependent on the manner in which controls are likely to be exercised in the future.

5. Biotechnology is also likely to be of greater value in detecting and monitoring pollution. The NRA consents the use of the commercially available "Microtox" system for some effluents, and is actively pursuing R&D into toxicity based consents using a range of biological material. It also has projects investigating the use of biological material as a monitor: for example, by attaching bacteria to an electrode such that changes in electrical current can be detected when it is induced by their response to changes in water quality. Such devices have considerable future potential.

6. The form of future regulation is thus important with regard to the future of such technology. With respect to the use of GOMs intended for widespread release, this will need to be controlled within a different framework from that required for the use of such organisms within systems or instruments where release is not intended.

Evidence from the Natural Environment Research Council

SUMMARY

The regulatory regime is quite properly strong on the environmental side. Bearing in mind the present state of knowledge on the impacts of genetically modified organisms on the environment, it is important from the point of view of public acceptance of the technology and the long-term competitiveness of the industry to adopt a cautious approach. However, it is also important in terms of competitiveness to ensure that, as knowledge grows, this is taken into account in the regulatory regime, enabling future relaxation of consent requirements where justified.

NERC INTERESTS IN BIOTECHNOLOGY

1. The NERC Mission is to advance knowledge and understanding of the natural environment, its resources, and the processes and impacts of environmental change, at all scales, and to enable better predictions of future change to be made. In fulfilling this mission, NERC plans, supports and carries out research and training in the physical, chemical and biological sciences, both in its own research institutes and units and in the universities. The results provide a sound scientific basis for environmental protection and conservation and contribute both directly and indirectly to national economic growth and wealth creation.

2. There are a number of areas of interface with biotechnology where NERC has a current interest. The main ones are as follows:

- (a) risk assessment of the release to the environment of genetically modified organisms
- (b) the use of genetically modified microorganisms to understand the natural processes of microbial ecology
- (c) use of baculovirus expression vectors for the production of model candidate vaccines, diagnostic reagents and therapeutics
- (d) the development of more effective viral pesticides
- (e) tree biotechnology
- (f) marine biology.

NERC undertakes or supports relevant research at a number of its own establishments (in particular the NERC Institute of Virology and Environmental Microbiology (IVEM), the NERC Institute of Freshwater Ecology (IFE), and the NERC Institute of Terrestrial Ecology (ITE)), and in the universities.

3. Scientists at IVEM undertook the first approved releases in the world of a genetically modified organism (a baculovirus pesticide). They have also been proactive in the area of public information and openness on the release of such organisms to the environment.

How and why is biotechnology important to UK industry?

4. Major areas of industry, particularly those which relate to the medical, veterinary, agricultural and chemical (eg, pharmaceutical but also other) areas, are being revolutionised by biotechnology both in terms of new products being produced and improvements being made to existing manufacturing and production practices. The leaders are the USA and Japan, although European (UK) and Far Eastern companies are also heavily involved. Although the number of products that have entered the market to-date is small, they are increasing year by year. It is important for UK industry to be able to lead and benefit from this increasingly pervasive technology.

What future prospects and opportunities does the technology offer?

5. It is only some 40 years since DNA was identified as the medium of genetic information. It is only some 10 years since biotechnology became a realistic and exploitable technology. Despite these short periods it is now possible to identify, sequence, and manipulate virtually any gene of any organism, and to characterise the various forms and properties of such genes and their products (natural or aberrant). Complete genome

sequences are being derived for man. selected plants and microbes. Very many viruses have already been completely sequenced. The study of genes and genetic variation is becoming a major growth industry for research and application (eg, identifying gene differences, disorders, and allowing novel product designs for vaccines, therapy, etc). The possibility of performing genetic changes and custom designing genes for particular prescribed functions (proteins, therapeutics, multiiprotein structures, new cellular activities, transgenic species, etc) will be realised at an ever-increasing pace over the next decades and hundreds of years. These opportunities will not be limited to any one species.

6. Completely novel processes and products (eg, those that cannot be made by traditional procedures) will become commonplace through the application of this technology (eg, chemistry, pharmacology, products for horticulture, other agricultural crops, renewable resources, livestock, medicines, etc). Biotechnological approaches to redressing problems of pollution will play an ever-increasing part in waste management as knowledge accumulates. The future prospects and opportunities offered by this technology in terms of advancing scientific knowledge as well as scientific applications will be enormous, almost certainly beyond current perceptions and visions.

Which developments in biotechnology raise issues of safety and how should they be addressed?

7. Issues of safety encompass both human safety, and environmental protection. Animal welfare is another, related, issue. There are both scientific problems and regulatory issues that need to be addressed. The following comments relate primarily to laboratory and field research. They do not address industrial and large scale research.

8. Worldwide, thousands of laboratory-contained experiments involving biotechnology are undertaken daily and without adverse consequences. In terms of human safety, the original fears and concerns that this technology induced at its inception were, with hindsight, certainly misplaced. The experience gained supports the self-assessment and reporting systems for such studies that have been in place in the UK for a number of years, administered and audited by the Health and Safety Executive (HSE). Where known pathogens and toxic products are the subjects of biotechnology, there are justified requirements for higher forms of containment and higher standards of safety. An effective consent process exists in the UK (also managed by the HSE) for the regulation of such work.

9. Laboratory studies involving micro-organisms generally involve a high degree of precision and predictability, both because of their limited genomes and because the technologies to introduce genetic changes are highly refined. For viruses and bacteria (including plasmids), it is possible to modify their genomes in a prescribed manner (eg by introducing a specific alteration to a specific place) so that no natural function is affected—unless that is what is intended. The alterations can be verified and, if necessary, monitored through a large number of generations, and analysed to document the stability of the changes and the consequences on the host (competitiveness, genetic stability, etc). This precision of laboratory research involving genetically manipulated viruses and bacteria, contributes to the predictability (hence safety) of such research.

10. For transgenic plants and animals, the same precision of introducing genetic changes (sites, copies, effect on resident genes, their flanking sequences and other genes) cannot be realised with presently available technologies (ballistics, virus or bacterial vectors, physical introduction of DNA, etc). It is also not possible to undertake a large number of generation studies in the laboratory to delineate the consequences of genetic changes in livestock for example. Of particular concern is the issue of animal health and welfare in relation to these issues, and the likelihood and realisation of unpredicted aberrant development or disease. Research into new DNA introduction technologies and a greater knowledge of the genomes of higher organisms are required to provide a solution to such problems.

11. Little experience exists concerning the impact of biotechnology and genetically modified organisms on the environment. Also, the types of studies that are being contemplated are of a different character to those that are conducted in contained laboratories.

12. Although similar comments concerning precision and predictability can be made for the genetically modified microbes that are to be used in the environment, as those used in laboratory research, the conditions that they encounter in the field cannot be mimicked in the laboratory. The predictability of their performance in the field is therefore less sure.

13. Field releases of higher organisms are in some cases more controllable than microorganisms, but different issues of safety arise, particularly for those higher organisms that can replicate and spread (eg plants that are dispersed and become "weedy") or that can transfer genetic information to other plants.

14. In the present state of knowledge on the impact of genetically modified organisms on the environment it is essential to retain an initial case-by-case evaluation system for field work. We support the recently enacted legislation in this area, administered by the Department of the Environment (DoE), and the regulations that have been established, involving such a case-by-case evaluation and consent approach. We also support the

opportunity provided in the future for categories of releases (eg involving particular organisms or manipulations for which adequate information is available) to be relieved from such consent requirements.

Should biotechnology be regulated by an industry specific regime?

15. The same generic considerations apply with respect to the materials and in relation to safety (human, animal welfare, environment), even though the scale of the problem and the forms of required containment may be different.

From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?

Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?

16. Products likely to be deployed in the environment, specifically modified viruses, bacteria, plants and animals, will generally have to be judged (regulated) vertically by their characteristics rather than by any surety based on the procedures that were involved in their preparation. This is due to uncertainties concerning their fate (interactions, dispersal, fitness, etc) and their genetic attributes. As already noted (para 10), for transgenic higher organisms, the procedures use in their preparation are insufficiently precise to allow predictions of their properties to be made. Even for microbes (para 9), although the genetic procedures involved in their preparation are precise, allowing greater predictability in terms of their genetic attributes, at this time the environmental properties of engineered organisms cannot be predicted with total certainty. This will come with experience derived from their use under proscribed circumstances.

What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry.

17. The UK is well placed to undertake research and development in the area of biotechnology. Critical to maintaining this position will be the need to continually review the situation and make appropriate adjustments to the regulatory regime in the light of experience.

18. The procedures now established by DoE and HSE and advice given to these Departments by the Advisory Committee on Releases to the Environment (ACRE) have been refined to the state that they function efficiently both with regard to the application and evaluation procedure, the establishment of a Public Register of proposed releases, and the opportunity for public input into the consent process. However, NERC has experienced one instance where, following consideration by ACRE, a delay in further consideration within Government to enable completion of the consent/licensing process, has caused a major hold-up in research. If industry were to experience a similar unaccountable delay, it could seriously affect its competitiveness.

19. Small scale laboratory research work in the UK, such as that supported in NERC Institutes, is unlikely to be over or unnecessarily constrained by the present biotechnology regulations. Field (environmental) trials involving biotechnology products are also unlikely to be unnecessarily constrained, provided all Departments can operate their systems in a timely fashion.

How best can issues of public acceptance be addressed?

20. NERC, through its involvement in the Biotechnology Joint Advisory Board (BJAB) has been concerned to obtain a better understanding of what determines public perception of biotechnology. We believe that the way in which biotechnology matters are often dealt with by the media presents a very unbalanced view of the potential benefits and disbenefits of biotechnology products and processes. BJAB held a seminar on this general area in 1992 and a report is being produced by the Economic and Social Research Council. NERC is currently working with other partners in BJAB to consider how to take forward this important but difficult area.

21. As regards releases to the environment of genetically modified organisms, NERC believes strongly in the need for oppenness, unless it is considered that there are good commercial reasons why total oppenness is not possible. The involvement of the Green Alliance in ACRE and the establishment of a Public Register of prospective releases are both positive moves.

Letter to the Clerk from Novo Nordisk A/S (J L Mahler)

Dear Mr Walters,

We wish to acknowledge receipt of your letter of 24 February 1993 explaining the set up of a Sub-Committee to look into the above mentioned topic. Our replies to your questions are as follows:

1. The present Government has had just one month in office and to the best of my knowledge has not indicated its specific perception of the importance of biotechnology. However, the Government has emphasised the importance of the contribution of competitive Danish companies and the importance of research and technological development for economic growth. Several new ministries have been established for just these purposes.

2. The deliberate release of genetically modified organisms is an area where Denmark has very little experience due to the ban of such releases between the first gene law (1986) and the revised gene law (1991). Although this ban did have an exemption possibility, it effectively prevented companies and authorities from gaining experience. Consequently, deliberate releases are still thought to raise safety issues, whereas contained use has become a matter of almost routine. It should be added that a few releases of genetically modified sugar beets and rape seed have taken place, while potatoes are presently being considered.

3. Yes. The gene technology law of 1986 was revised on minor details in the years following its enactment and was completely revised in 1991, when Denmark implemented the EC directives 90/219 and 90/220.

4. Yes, if by "general release" you mean "deliberate release".

5. It is horizontal and in fact was the first gene technology law in the world in 1986.

6. Our competitiveness was damaged around 1986, because the Danish authorities did not have any experience and consequently delayed our start-up of the production of human insulin and human growth hormone. However, since then things have much improved and presently we consider the burdens upon us in Denmark as technically equivalent to those found in the rest of the EC, USA and Japan. Despite differences in regulatory structure, all contained use operations essentially have to comply with OECD guidelines.

7. Contained use is publicly accepted, and deliberate release of plants is almost accepted, because the public have confidence in the Danish regulations and in the companies involved.

8. Yes, by enacting the gene technology law of 1991 with decrees coming into force at the same time or later, so that by now Denmark has received the approval by the Commission's legal services of the correctness of the implementation.

We trust that the above information will be of help to the Sub-Committee.

J L Mahler

External Affairs

Letter to the Clerk from David Shapiro Esq, Executive Secretary, Nuffield Council of Bioethics

The Council at its meeting on 1 April considered the questions posed by Sub-Committee II of the Select Committee on Science & Technology on the Regulation of the UK biotechnology industry and global competitiveness. The Council wishes to make the following points:—

(1) The Council is in no sense a regulatory body; the Council's term of reference are set out in the attached Annex.

(2) Question No 11 is the one Question within the Council's terms of reference. The Council's view is that public acceptance is best addressed by openness and frankness on the part of industry and the regulatory authorities. Public education needs to be based on the assumption that there is sufficient public interest for any work in this area to be based on serious intellectual standards. The ethical point is that in seeking public trust the industry and the regulatory authorities should practise the highest standards.

Evidence from Professor David Onions, University of Glasgow

SUMMARY

Regulation is not the limiting factor in the exploitation of biotechnology in the United Kingdom. Regulation is set in a European framework and similar systems operate in the United States of America and Japan.

Safety evaluation should be seen as part of the total quality management of product development, rather than as a barrier in getting a product to the market place.

The factors constraining the development of biotechnology in the United kingdom are:

1. Underfunding of university science and a poor level of scientific education in the general population.
2. Conservative capital markets that do not encourage exploitation of new areas of technology.
3. A cultural barrier in our universities that inhibits commercial development of scientific ideas.

QUESTIONS ON WHICH EVIDENCE IS INVITED

1. *What is your interest in biotechnology?*

I am a co-founder of a profitable biotechnology company *Quality Biotech Ltd.* involved in the safety evaluation of monoclonal antibodies, recombinant DNA products and vaccines.

I am on the scientific advisory board of *Pharmaceutical Proteins Ltd.*, a company producing transgenic sheep expressing pharmaceutical proteins in their milk.

I am a member of the DOE's Advisory committee on The Release of Recombinant Organisms into the Environment (ACRE).

I have been an expert witness on the Ethics of Gene Therapy Committee.

In addition, as a Professor of Veterinary Pathology at Glasgow University I am involved in research in biotechnology. The Department was recently awarded a grade 5 with commendation in the UFC Research Selectivity Exercise primarily for work on the molecular biology of cancer and viruses. As part of this programme of research, the Department has projects on recombinant vaccine development funded by industry.

2. *How and why is biotechnology important to the UK industry?*

The rapid development of recombinant DNA technology over the last decade has spawned a new industry that is likely to have as profound effect on our lives as the parallel revolution in information technology. It is estimated that by 2003 the pharmaceutical market will be worth $250 billion and at least 10 per cent of these products will be directly produced by biotechnology.

3. *What future prospects and opportunities does the technology offer*

An assesssment of the impact of biotechnology for a period longer than 15 to 20 years is almost certainly bound to be incorrect since, changes in technology and external pressures on economic and social development cannot be predicted. In the short run the prospects of biotechnology will be dictated by public acceptability and the capabilities of the technology.

3.1 *First generation technology*

First generation technologies are those currently entering the clinic or are nearing clinical or field trials

Monoclonal Antibodies: The technology for the production of monoclonal antobodies is changing but already first generation products are being used or developed for:

1. Cancer imaging and therapy.
2. The treatment of immune disorders particularly autoimmune conditions.
3. The treatment of chronic infections and acute toxic shock syndromes.

Human Proteins (Cytokines): The first generation products of recombinant DNA technology have been normal human proteins whose genes have been expressed in bacterial or mammalian cells grown in fermenters. For instance products like G-CSF are natural growth factors for precursors of white blood cells. These defense cells are greatly reduced in numbers during cytotoxic chemotherapy for cancer. Providing the natural protein G-CSF during cancer therapy can ameliorate the severe effects of the cancer chemotherapy by restoring white blood cell numbers.

Recombinant Vaccines: Traditional vaccines are either attenuated living counterparts of the natural, wild type virus or bacterium or are inactivated (killed) versions of the wild type organism. These traditional vaccines depend on the ability to grow the organism and on empirical knowledge of how the immune system effects protection. These approaches are impossible or inadequate for many pathogenic micro-organisms including hepatitis-B virus and HIV. Similarly parasitic infections have proved resistent to conventional vaccine technologies and these infections are the source of the majority of chronic diseases in the developing world.

Recombinant DNA technology permits the expression of specific parts of a micro-organism so that sub-unit vaccines can be developed. This approach has already been successfully applied in the development of hepatitis-B vaccines. Modified live vaccines can also be developed by removing genes from micro-organisms that affect their virulence and vaccines based on this principle are already licensed for use in veterinary medicine. The next stage of will be to use one micro-organism as a vector to express the immunogenic proteins of another micro-organism.

The 3 product areas described above have not aroused much controversy and the procedures required to ensure the safe development of such products are understood. The production of transgenic plants and animals arouses far wider public concern although the potential benefits of these technologies are very large.

Transgenic Plants: Most developments in transgenic plants have been concerned with the introduction of genes that have the following properties:

1. Genes conferring resistance to specific herbicides so that weedy plants can be removed from a field without affecting the crop plant.
2. Viral genes that when expressed in plants may confer resistance to virus infection.
3. The introduction of genes that might confer resistance to insect pests.
4. Genes that alter the metabolism of plants for instance, genes that alter their protein composition or their ability to fix nitrogen.
5. Genes that alter the pigment or other aesthetic properties of plants.

The concerns over transgenic plants have revolved around two main issues. The first is a scientific concern that, plants with altered characteristics might be produced that could establish themselves as new weed species or in some other way have a profound effect on the environment. For instance, if a gene for herbicide resistance and altered growth properties were transferred by gene flow from pollen into a wild species, a potentially new weedy species might be produced. It is the role of the ACRE committee in the UK to advise the Ministry of the Environment on the safe release of such plants.

The second concern expressed by some, is that the new technologies will concentrate economic power in international seed companies and will lead to products being produced without regard to a cost benefit analysis, where the major costs are the impact on the environment. This is not a viewpoint I share but I recognise that there are social and environmental aspects of transgenic technology that extend beyond the immediate question of whether the technology is safe or not.

— *Transgenic animals:* It is possible to produce animals expressing foreign genes by micro-injecting those genes into the early, single cell staged embryo. The resulting animal may express the foreign gene and will pass this gene onto its offspring. This technology will be superseded by the ability to grow embryonic stem cells from many species. This system already developed in mice, permits cells capable of producing a viable embryo to be grown in tissue culture. Genes can be deleted from these cells as well as introduced and methods for targeting gene insertions to particular sites in the chromosomes are improving. These techniques have many applicatons:

1. *Disease models:* Transgenic mice can be produced that develop specific diseases. For instance my own group has been introducing human cancer causing genes into mice so that we can understand the multiple gene interactions necessary to cause cancer. We believe that these approaches may eventually lead to, techniques to switch off or modify the effects of cancer genes within cells. Recent progress in cystic fibrosis research has depended on the ability to "knock-out" normal genes in the mouse to produce lines with cystic fibrosis. These mice have been used to develop techniques for gene therapy for this distressing condition.

   Like all animal experimentation, there are important moral question that attend this form of work. In this country, these questions are taken seriously both by the scientists involved and by legislators. We are fortunate in having a Home Office Inspectorate that is both informed and impartial and has ensured that this new branch of technology has not proceeded at the expense of the welfare of animals.
2. *Farming of Pharmaceutical Proteins:* It is now possible to express human proteins in milk or other tissues of animals so these can be harvested. Their are potentially large markets for certain blood products expressed in this way. The concerns over this technology are both ethical and relate to the problems of safety of products derived from whole animals.
3. *Improved farm livestock.* Introducing genes that confer resistance to infectious disease could improve the welfare of animals as well as having economic benefits. I am less sanguine about the short term prospects of manipulating the physiology of animals through genetic engineering, to confer advantages in production.

Second generation technologies

Second generation technologies will extend the immediately obvious biological applications and may result in new materials new methods of manufacture (nanotechnology). However, the impact on human health is likely to remain at the forefront of commercial and public interest. Among the areas that are likely to be of importance are:

1. The second generation recombinant products will involve modified human proteins or completely synthetic analogues that have a range but not all of the activities of the native protein.
2. Techniques for product discovery may involve rapid molecular evolution and natural selection *in vitro,* mimicking the procedures used to generate genetic change in natural evolution.

3. The human genome project will have an impact on genetic diseases and on identifying new therapeutic targets. The fruits of this project will depend on new methods of data analysis and will require further basic research in the control of gene expression and organisation.
4. Somatic Gene therapy will become widely established extending beyond the correction of inherited gene defects. Methods for correcting the expression of cancer associated genes (oncogenes) will be attempted using ant-sense and other technologies.
5. Germline gene therapy will become technically possible.

4. *What developments in biotechnology raise issues of safety and how should they be addressed?*

The problems of producing recombinant proteins or monoclonal antibodies in animal cells, bacteria or yeast raise problems of safety from microbiological contamination of those systems. A clear set of guidelines has evolved for ensuring the safety of these products from microbiological contamination. These guidelines have been formulated as a result of a dialogue between the producers, safety testing companies like *Quality Biotech* and the competent regulatory authorities and their advisers. The basic principles of ensuring safety are to adopt the storage of characterised cell banks from which the products are derived, to test the product at various stages of manufacture for freedom from micro-organisms and finally to validate the downstream purification systems to demonstrate that they would remove or inactivate viruses and other micro-organisms.

The safety of monoclonal antibodies and recombinant DNA products is approached as for other pharmaceutical products through animal tests and staged clinical trials. Because recombinant DNA products are derived from human genes they are probably intrinsically safer than most synthetic pharmaceutical products. In early studies, monoclonal antibodies produced from mouse cells raised concerns that the mouse proteins would induce a harmful host immune response. This possible effect is now being side stepped by "humanising" the antibodies or otherwise modifying them so that the human immune system does not recognise them as foreign.

The release of recombinant plants, viruses and to a lesser extent animals raises a different set of concerns in that, novel combinations of genetic information are being released into the environment where it may be difficult or impossible to control their spread. Permission is required for the release of a recombinant organism (Directive 90/220/EEC). Each case has to be considered on its merit based on the experience of other cases and from laboratory data on the properties of the organism. In turn this requires that the competent authorities have a monitoring system to evaluate the results of a release. Such systems are in place in the UK.

5. *Should biotechnology be regulated by an industry specific regime?*

No.

6. *From a technical point of view is horizontal regulation better than vertical regulation?*

The question has little relevance. Both forms of regulation operate for pharmaceutical products whether derived by biotechnology or not. The safety of a recombinant protein or vaccine derived from genes introduced into mammalian cells must be evaluated as such (in terms horizontal regulation). In addition the specific properties of the product in terms of safety and efficacy must also be determined (vertical regulation).

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

As indicated above I do not accept that product approval is exclusively "horizontal" or "vertical". Both the product and process of manufacture are relevant to safety evaluation.

There may be some problems arising out of parallel consideration of a product by more than one committee. For instance the release of a recombinant vaccine will be considered by the ACRE committee for its effect on the environmentand by the relevant MCA committee for its efficacy and safety. Similarly, the interim arrangements for considering gene therapy protocols have not yet taken on board the requirements and experience gained in regulating other recombinant DNA products and procedures.

8. *How do current regulations compare with those of other competitor countries?*

A broadly similar regulatory framework has evolved in Europe, the USA and Japan although there are important differences in procedures. As markets become international it becomes cost-effective to devise a testing programme that meets the requirements of all of these major markets.

In the European Community legislation initiated in 1984 began the process of regulating high technology biotechnology products, including monoclonal antibodies and products derived by recombinant DNA methods. The competent authorities of member states were obliged to consult with each other and the Committee for Proprietary Medicinal Products (CPMP) concerning the use of products derived by biotechnology. With the onset of the single market a three tier system of regulation operates. National procedures are limited to applications to a single member state but a decentralised system, covering the majority of medicinal products, will reflect mutual recognition of approval between certain member states.

For high technology medicinal products derived by biotechnology, a centralised procedure is compulsory. It is proposed that applications for authorisation will eventually be submitted directly to a European Agency for the Evaluation of Medicines which will encompass the functions of the Committee for Proprietary Medicinal Products (CPMP) and the Committee for Veterinary Medicinal Products (CVMP).

9. *What are the consequences or likely consequences, of the regulatory regime on competitiveness of the UK industry?*

The regulatory regime will become increasingly harmonised in Europe. Over zealous local regulation of biotechnology, as occurred in Germany, can have dramatic effects on industrial location but, as the regulations are harmonised within Europe, this will become a feature of the past. I would have thought, however, that trade protection including the USA's requirement for partial local manufacture of products, will have a more profound influence on investment decisions.

There is always a tendency to view regulation as a negative influence. This is often expressed by bench scientists involved in R&D and sometimes by product development managers of ailing companies. Careful regulation should become part of the total quality management of a product. It has been my experience in dealing with biotechnology companies both here and in the United States that, those companies that have instituted safety evaluation as an integral part of their development have been the most successful. We should not forget that a major disaster brought about by an unsafe product would dramatically affect the public's acceptance of this nascent industry.

There are concerns about the length of time required to get a product from the final development stage to the market. This has been particularly noticeable in the United States of America. It is essential that the local competent authorities and the European agency, when it is formed, have the resources, particularly in qualified persons, to ensure the rapid processing of applications. However, much of the costs and delays affecting development relate to clinical trials which are no different for biotechnology products than for conventional products.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

There are far more important factors affecting the exploitation of biotechnology. There is however a case for more streamlined procedures for the licensing of products with small markets.

At another level the burdens now placed on University research by regulations is some cause for concern. In order to prepare a recombinant vaccine for release into the environment it would be necessary to undertake the following:

1. Obtain appropriate grant funding.
2. For the first phrase of laboratory based studies, apply for permission to work with recombinant DNA and conduct a safety and environmental impact assessment of the particular laboratory project.
3. Undertake a COHSH evaluation for products and procedures not covered in 2.
4. Apply for permission to work with radioactive isotopes and institute correct monitoring procedures.
5. Apply for a Home Office Project and Personal Licence to conduct a trial with the vaccine.
6. Apply through ACRE for permission to relase the recombinant vaccine.

I do not object to any of these procedures but university science is chronically underfunded and not able to meet the direct financial and manpower demands that these regulations require.

11. *How best can issues of public acceptance be addressed?*

By education, openness and ensuring the safety of the products. The ACRE committee has been a good model. Public notification of releases is required and the dissemination of information to relevant local groups is encouraged (eg bee keepers in the case of the releases of transgenic plants).

12. *What other factors do you think will play a crucial role in the competitiveness of the UK biotechnology industry?*

This is the most important question raised by the committee. In my view the most important factors are:

1. *Education at all levels.* Science is inadequately taught in our schools. I suggest it is necessary to give differential pay awards to teachers in subjects like science and mathematics to attract them into the service. A senior executive of an American biotechnology company recently told me that they would consider opening plants in Singapore not because the labour was cheaper than in Europe but because school leavers had a high educational standard.
2. *Investment in first rate, basic, science.* Biotechnology does not exist in a vacuum it depends on innovation and understanding at all levels in science. Few would have predicted that a group of American academics studying the restistance to infection of bacteria by some obscure bacteriophage would discover the enzymes that initiated the biotechnology revolution. You cannot direct science down particular paths. Fund good people and fund them well.
3. *Permit venture capital investments in start up companies to be written off against tax.* Similar laws were an important ingredient in developing the early biotechnology industry in California.
4. *Change the stock exchange rules to encourage blue skies research companies.* We have one of the most conservative venture capital markets. In the United States of America large funds are raised quickly to exploit new ideas in biotechnology. Most of these companies will fail but one or two will become the new *Genentechs* or *Amgens*. It is noticeable that among the woefully few biotechnology companies in the UK, most are going public in the USA.
5. *Change the academic industrial relationship.* This is a complex subject which has much to do with cultural attitudes in the United Kingdom. It deserves serious comment but is perhaps most simply illustrated by two anecdotes. The first concerns a friend of mine, an American professor of microbiology who once lamented "you know I am the only chairman of a microbiology department in the United States who is not a multi-millionaire". The second concerns the response from a senior university officer when I first suggested forming a biotechnology company "Well David this is the sort of thing we are supposed to be doing but there are problems, we must not make other academics jealous".

Evidence from E R Orskov, OBE, Rowett Research Institute

My interest in biotechnology is that it could assist in solving some problems of animal production. There is, however, a lot of confusion here. What is biotechnology as distinct from Animal Science?, Is it only a word that helps some laboratories to give the impression of working on some magical components of life sciences?

In recent years, however, the public perception of biotechnology has suffered a great deal and I think the people pushing some technologies are largely responsible for this state of affairs which in the long run can damage the uptake of good and relevant science.

First of all progress in biotechnology must be problem led and not what so often happens biotechnology led. Let me illustrate this with a product such as Bovine Somatotrophine (BST) cover name for Growth Hormone as a method of increasing milk yield. First of all the development of this product was certainly not problem led as there was and still is overproduction of milk and milk product.

It can only be exploited biologically if the animals are given more concentrate or grain which could at least theoretically be used for many other purposes eg, human food, pig food or industrial raw material.

What was equally important here was public perception of hormone or hormone derivatives in milk. This can probably be disproved but whatever it is the public perception is decisive in determining the product purchased. Thus since there is really no adult requirement for milk, introduction of such products could seriously damage milk consumption in the EEC or in the UK. At the moment these companies are selling or trying to sell their products in developing countries where there may be shortage of milk but no concentrate to feed to ruminants.

I believe that government funding of so-called biotechnology must pay attention to this. There are many problems both plant and animal related which could be solved particularly those associated with diseases such as BSE, Foot and Mouth disease and countless others. If the biotechnological research is not focussed on problem solving I think we will have an uphill battle in how to exploit it. We do not need animals which grow faster and become bigger, we need perhaps animals which can make use of wasted feed better eg, straw.

On the whole I feel that biotechnologists, in order to achieve funding for their work must clearly state their problem solving objective. If that is done I believe there will be little problem in exploiting the results but if, as with BST, it was aimed at a non-problem which had only marginal production advantages and which the public perception was and is such that it could seriously damage the dairy farming industry were it ever to be released.

Evidence from Professor J W Parsons, Dean of Biological Sciences, University of Aberdeen

The following comments have been prepared by members of academic staff in the Faculty of Biological Sciences who are actively involved in Biotechnology.

Question 1. What is your interest in biotechnology?

We have two major interests in the impact of regulation on the UK Biotechnology industry. Firstly, through undergraduate and postgraduate training programmes we are major suppliers of trained personnel to the industry. Part of our postgraduate training involves on-site re-training of industrial staff. The health of the industry affects the employment prospects of our graduates and also the potential for us to interact with industry to ensure that the changing research face is transmitted to industry.

Secondly, we are an established centre for environmental research assessing the potential risks associated with the release of genetically-engineered microorganisms and for work on genetically engineered fish and the biotechnology of production. Tight regulation has the potential to harm the small-scale experiments that are essential in academic environments to assess the scale of the risks associated with the release of genetically modified organisms. Further, if large registration costs are applied to such work, eg in obtaining permission from the DoE to run an experiment, then only wealthy centres will be able to carry out such research or there could be a substantial drain on funds available for environmental research. Biotechnology research is itself very expensive; to apply extra costs through licensing will cripple it. Inevitably such research will only be conducted in industry itself. It is in everyone's interest that such risk assessment be seen to be carried out independently.

Question 2. How and why is biotechnology important to UK industry?

With the decline of the heavy engineering industries in the UK one of the few industries to remain profitable is that of pharmaceuticals. This industry has a well-established safety record. However, the next generation of drugs are unlikely to be generated/identified by the methods that have been used in the last fifty years (random screening against whole organisms). Biotechnology in the modern sense has the ability to deliver highly specific targets for screening drugs. This has enabled the efficacy against the target protein to be investigated independently of considerations of delivery to the target. This two stage process has allowed a much larger range of compounds to be investigated and has stimulated work on drug delivery, such as the development of liposome technology. Such high specificity is enabling greater refinement in drug screening and in drug modification and will facilitate the development of new therapeutics agents.

Question 3. What future prospects and opportunities does the technology offer?

Biotechnology and the environment: Biotechnology has already delivered novel bio-degradable plastics, has shown the potential for bio-remediation and has developed biological pesticides which avoid the use of chemicals which persist in the food chain.

Question 4. Which developments in biotechnology raise issues of safety and how should they be addressed?

All industries give some cause for concern. In recent times the issue of maintaining a clean environment whilst encouraging manufacturing output and agricultural productivity have been the major issues. Biotechnological industries are faced with the same issues since on the one hand they are potential polluters and on the other they may offer solutions to the waste problems experienced by others. Risk assessment is the better way forward for the biotechnology industry but this can only be undertaken, in the context of the environment, if there is more emphasis on research on the impact of "biotechnological processes" on the environment.

Question 5. Should biotechnology be regulated by an industry specific regime? and

Question 6. From a technical point of view, is horizontal regulation (where a product is judged through a process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?

In our view vertical regulation is most appropriate for biotechnology. This is the case also in the USA. There is a strong danger that restrictive, horizontal regulation may lead research and development to be transferred to countries which have more lax regimes. Reasonable regulation which is in the public interest is desirable whereas excessive regulation will undermine the confidence of the industry. Once the industry is crippled, the research culture, to which biotechnology is particularly attuned, will be damaged irreparably. Biotechnology in the USA is stongly based upon venture capital and involves small firms. The UK has done less well in this area due to the lack of venture capital. However, the modest successes are likely to be undermined if regulatory costs are not kept to reasonable limits.

Question 11. How best can issues of public acceptance be addressed?

The public has readily accepted the beneficial aspects of biotechnology for the last fifty years. Common foods (cheese, yoghurt, beer) are all produced by microorganisms as are antibiotics and many steroid-based drugs. The new phase of biotechnology is unlikely to engender any greater risk to the public than those to which they have been exposed for the last fifty years. Furthermore, advanced biotechnological products are rigorously tested at the present time and are adequately regulated by current laws. The good safety record of the industry, and the beneficial record of biotechnology, must be emphasised. Inflammatory and irresponsible journalism must be combated by better education of the public. Notable moves in this direction have been made by many of the quality newspapers and by some television channels, but there is little evidence of such responsibility by the tabloid press.

Question 12. What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?

The major problem faced by UK industry is the poor contact which it enjoys with the wider academic community, which represents a major intellectual resource. Companies are dissuaded from active interaction by the failure of successive governments to make industrially-funded academic work attractive to industry through tax concessions. This is in marked contrast to Japan and the USA where mechanisms are used to engender a collaborative process between the academics and the industrialists. Biotechnology exploits fundamental advances in biology. To be successful in this there must be a dynamic interface between the two communities.

Letter to the Clerk from Professor Sir Keith Peters, Regius Professor of Physic, University of Cambridge

I am responding to your enquiry of 22 February and rather than address the specific questions that you have set out I hope you will find it acceptable if I refer you to the ACOST Report on Biotechnology which I chaired. I believe most of the issues that you have identified were raised and various solutions proffered. In the ACOST Report, for example, we argued strongly that a biotechnology product must be judged by its characteristics; it is illogical to do otherwise.

The Government have responded to the ACOST Report, but I think the critical issue is the extent to which its recommendations have been implemented. This is an aspect that the Select Committee may wish to address.

Evidence from Pfizer Ltd.

1. *What are your interests in biotechnology?*

Pfizer is a major, multinational pharmaceutical company and, as such, has a significant interest in new technologies relevant to the discovery and production of new therapeutic agents.

Pfizer has heavily invested (both in research and production) in what might be described as conventional microbial technology. This has long been a major interest and, for many years, citric acid and other specialty chamicals produced by fermentation, were important products for the company. Pfizer first entered the pharmaceutical area as a key player in the development of mass production methods for penicillin and, since then, has been prominent in the discovery and development of several other microbially derived antibiotics, notably members of the tetracycline series such as doxycycline. More recently, microbial biosynthetic techniques have been employed to produce new anthelmintic agents and soil screening and fermentation development remain one of our approaches to the discovery of new therapeutic agents.

Currently, nearly 150 molecular biologists, based either in the UK or in the US, are involved in biotechnology research for the company. The main interests are the uses of gene manipulation techniques for:

(a) target production (human receptors and enzymes) as screens in the discovery of drugs.

(b) production of biological factors as therapeutic agents (growth factors etc.)

(c) assessment of new genetic therapies.

Animal cell culture techniques, often using genetic engineering technologies, provide the basis for many screens for novel active agents.

2. *How and why is biotechnology important to UK industry?*

Biotechnology (the application of molecular biology techniques to industrial processes) is an expanding industry, underpinning an increasing proportion of biochemical research and development within the pharmaceutical, agrochemical and other industries.

Fermentation technology has made considerable strides in the past decade, exploiting our increasing knowledge of microbial physiology, metabolic regulation at both the nutrient and genetic level, and the application of computer process control. The commercial production of a wide range of biologically active medicines, chemicals and enzymes has been achieved.

The UK has an enviable record in this area with a number of excellent academic microbiological/fermentation groups; appropriate funding to maintain this position is essential.

In addition, synthetic modification of compounds unachievable by chemical methods, and resolution of chiral mixtures of drugs (essential in the current regulatory climate), has also been obtained through the renewed interest in biotransformation. The UK leads the world in this area, with several academic centres involved (eg the Universities of Exeter, Warwick and Kent).

Another avenue of biotechnology, plant cell technology, has the potential to provide access to plant-derived compounds with unique and exciting biological activities (as seen in the product of the American Yew, taxol). Again, rapid progress is being made in this area, in which, however, the UK is poorly represented: the only major UK research group, Plant Sciences Ltd, an offshoot of the University of Sheffield, was recently acquired by a US company.

One of the earliest biotechnologies, natural product screening has seen a recent upsurge in activity, especially with tropical fungi, and while the UK is well represented, many other groups worldwide are developing similar technologies. In all the areas of biotechnology, the role of national culture collections as repositories for the microorganisms, cell lines, and plants which provide the genetic heritage for much research should not be overlooked. The UK has several such world renowned collections (eg IMI, NCIMB, and Kew Gardens).

At the same time, new molecular biotechnologies are providing new challenges and opportunities in medicine: novel biotechnology applications such as gene therapy are set to revolutionise the treatment of a substantial number of previously untreatable diseases eg cancer, possibly AIDS. It raises the possibility of reshaping our environment, through the development of new methods for biological control and waste treatment. It also promises to provide new routes to the synthesis of important chemicals in large quantities (through the use of specific biotransformations).

In short, biotechnology is providing alternative ways of producing both established and novel products. Moreover, our increasing awareness and understanding of how biological systems operate provide increasing opportunities for the exploitation and harnessing of these processes for the well-being of our nation. Without substantial investment in this area, the UK will effectively be excluded from this revolution, equal in importance to that occurring in the information technology area.

3. *Future prospects and opportunities*

In the pharmaceutical arena, biotechnology is providing a wide range of new opportunities, including:

- Gene therapy applications
- Clinical diagnostics for cancer, AIDS etc
- Preventative medicine, stemming from diagnostics
- New, safe routes to vaccine development, using recombinant antigens, not attenuated live organisms
- Resolution of chiral mixtures through biotransformation

In the wider world, everyday applications include:

- Forensic science (DNA fingerprinting etc)
- Biotransformations (high value chemical production; lower grade waste management, recycling etc)
- Food processing (transgenic plants etc)
- Biological cleaners (washing powders etc)
- Insecticide resistant and insect resistant crops
- New nitrogen-fixing cereals

4. *Safety*

Basic gene manipulations present little hazard. The technology is well worked out and well-understood, at both a theoretical and practical level. The work is usually performed in a contained environment, under appropriate guidelines provided by the HSE.

Larger-scale production of biological materials is carried out under strict provisions: in the pharmaceutical industry the safety of the worker is matched by the care and attention which we pay to the product, which has to pass strict quality control before administration to man.

In controlled release applications (eg release of biological insecticides etc), care has to be taken to ensure the protection of the environment. Again, this environmental protection is already provided by specific Controlled Release Regulations administered by the DoE.

The original, pioneering regulations in the UK from HSE on genetic manipulation served both academia and industry well; innovation was not stifled, nor were there any known incidents. The new regulations (implemented on 1 February 1993), while reflecting tighter EC directives, were in their original form severely restricting, and undoubtedly put the UK at a disadvantage to the US and other European states. After considerable UK pressure the regulations were amended and in general should now allow innovative research in the UK to continue to progress, while providing the necessary safety standards. Large scale manufacture is also covered in these regulations (as well as in many others), and, coupled with the necessity for sterile operation, current processes are covered by more than adequate safety procedures. It is essential that the UK operates on a "level playing field" with other EC countries and the US in regard to such controls.

5. *Industry-specific regulation*

Biotechnology is a concept which covers a wide variety of biological sciences, many of which have been in existence for many years. There can be little sense in "industry-specific" regulations in this context.

Only recently has genetic engineering entered the arena. At the research level, worker, public and environmental safety requirements are the same, and genetic engineering, along with other biotechnology processes, are carefully monitored within industry. Again, on a manufacturing scale, many different regulations and in-house operational requirements already exist to ensure safe operation. We already have specific regulations covering genetic manipulation, which comprise "industry-specific" regulations, which operate well.

There is no need for additional "industry-specific" regulation.

6. *Horizontal vs. Vertical Regulation*

The present genetic manipulation regulations primarily operate on a horizontal (ie process-related) level. This is probably the best focus for research applications, since the processes which we use are composed of large numbers of individual but repetitive manipulations, which can usually be covered by generic protocols.

It is difficult to restrict regulation to a single modality: horizontal or vertical. To take an example, aflatoxin, a most potent carcinogen, can be produced by a safe fermentation process, but you would have to know what you were making to operate safely. Likewise, production of a harmless antigen for vaccine purposes by *Vaccinia* expression systems, which have to be handled with care, would require more than a simple knowledge of the product. In the assessment of genetic engineering projects by the Brenner system, account is taken of the risks associated with the process of production (covered through access/expression risk factors) *and* the effect of the gene product (covered through damage factors).

In many cases, provided biotechnology products meet established criteria for purity and efficacy, there should be no risks associated with the end-products of the biotechnology process.

7. *Vertical or Horizontal*

Provided the product meets the quality, safety and efficacy standards required, the process by which it is obtained is immaterial to its safety. Thus, vertical regulation is what the regulations for a manufacturing process should be based on. As indicated above, many research processes are best regulated horizontally, although here other concerns such as the proprietary nature of the processes themselves suggest that the minimum regulation possible would be the best situation for industry.

8. *Competitor Countries*

Our regulations are consistent with those governing other countries within Europe. What differs is the degree to which they are enforced. The over-rigorous interpretation of rules and regulations has effectively killed the German biotech industry, while the large-scale production and use of genetically-engineered products is allowed in neighbouring Denmark, Holland, Belgium and France. The UK is probably further forward in implementing genetic engineering regulation than most countries, but is probably treading the middle path, having more restrictions than proposed in some EC countries, and less than in others.

We compare very unfavourably in this regard to the US, where the government pays great attention to the views of the biotechnology industry associations (cf. the reluctance of President Bush to ratify the Genetic Diversity Treaty). It's very difficult to regulate an industry which thrives on innovation without irreparably stunting its growth: the US regulations are much more flexible than those in Europe, and are based on vertical (product) rather than process regulation.

I'm not aware of the regulations in the Far East.

9. *Regulation vs Competitivity*

(a) **Research:**

The more you regulate, the less industry innovates. Biotechnology thrives on the testing and application of new ideas. Unless the right regulatory environment is provided, research won't flourish. It is perhaps no coincidence that the majority of biotech companies are in the US, with California predominating.

However, the new UK genetic manipulation regulations should not unduly restrict research in the UK, with the exception of the following:

- Time taken for consent from HSE for some aspects of GM work (up to three months), which could lead to lost opportunities;
- Breaching of confidentiality by the requirement to provide information relating to the genetic manipulation work, with the consequent possibility of invalidating patent claims;
- Fees are charged for consents, which in the current economic climate could reduce research in Universities.

(b) **Product development:**

The major market for biotech products is the US. Regulation in the US is highly product oriented, in the pharmaceutical industry governed primarily by the FDA. There are clear criteria governing purity, batch-to-batch consistency etc, which drive product development: a case in which regulations assist the industry.

(c) **Investment:**

Again, the only market with sufficient venture capital investment is the US. From European pension funds to Japanese banks, everyone acknowledges the innovation displayed by the US biotech industry: and innovation attracts more investment.

(d) **Location:**

Biotech industries gravitate to centres of academic excellence. The only SE-quoted British biotech company is BBL, who have the great advantage of being close to Oxford University. In the US, wherever there are good science-based universities, biotech companies abound (eg Stanford & UCSF spawned Amgen and Genentech; MIT spawned Biogen).

An extremely good example of a case where the regulatory environment had a major negative influence on biotechnology growth was when the Boston city council outlawed genetic engineering. Immediately, scientists packed their bags and set up labs in London and Heidelberg, carrying on with their work as usual and conveying a great boost to European and British molecular biology. Excellence amongst the scientists drives progress in the industry.

10. *Dangers of the present regulatory regime*

Many US-based pharmaceutical companies carry out their R&D in the UK, but perform their manufacturing elsewhere. As an American company, Pfizer recognises that pharmacology in the UK is amongst the best in the world, and has no hesitation in investing wherever discoveries are made. The same applies to biotechnology: investments will be made wherever science makes the breakthroughs. In this respect, it's interesting to note that many UK companies (eg Glaxo and SKB) carry out significant swathes of their biotech research in the US. Over-regulation has also driven German companies to move their recombinant DNA research to the US. If the UK becomes over-regulated, companies will no doubt also move similar work to the US, taking away jobs and wasting the investment in our science base.

Of equal concern is the reduction in basic University research in the UK which is happening through funding cut-backs. If training for research dries up, there will be no-one to undertake the research and development in the first place!

11. *Issues of Public Acceptance*

These are best dealt with at a governmental level. There is too much blowing in the wind, and not enough support for innovation in the UK. In the US, biotechnology is viewed, like every other technology, as basically good until demonstrated otherwise. Here, the public are less at ease with technology: they don't understand it. Movements like the Greens exploit people's irrational fears, while the Government avoids key issues. Too much politics, not enough action. The Government needs to show their confidence in the UK biotechnology industry, through support of the initiatives of the various industry associations (CBI, BIA, APBI).

A key element in building acceptance is education. There are too few teachers in our schools who actually understand biotechnology themselves. The industry seeks to heighten public understanding of the science and increased awareness of its benefits, and needs the support of the UK's education base in this.

12. *Competitivity*

The key issue surrounding biotech competitivity is investment: investment in the science base; investment in the research infrastructure within Universities; venture capital investment to commercialise UK discoveries. If this is backed by a positive regulatory climate, the innate innovation and skill inculcated in the British scientist should shine through.

The UK biotechnology industry is as able as any other to exploit and develop new commercial opportunities from recombinant DNA research.

Letter to the Clerk from Dr B A Johnson, Potato Marketing Board

I have been asked to reply on behalf of the PMB, which represents Great Britain's 17,000 potato growers, to your request for comments to the Select Committee on Science and Technology. I shall address each of your questions in turn.

1. *What is our interest in biotechnology?*

As a major investor in Potato Research and Development the Board has a real interest in Biotechnology and its potential contribution to the industry.

Our main interest in biotechnology is expected to be in the growing of transgenic potatoes and in the exploitation of their products. We anticipate that breeders will be introducing genetically modified varieties of potatoes offering improved quality characteristics and pest and disease resistance through the use of techniques which are faster, more selective and more targeted than those employed in conventional breeding. We also have a strong interest in the development of novel uses of potato, such as altered proteins and starches.

2. *How and why is biotechnology important to UK industry*

Biotechnology is a rapidly expanding sector, with the potential benefits, particularly in the area of crop protection of great economic and social importance. Consumers and the public at large want to see a reduction in chemical input to control pests and diseases in the agricultural crop. This is true in the US, Japan and Europe. The current research to identify genes and their insertion into plants is being carried out worldwide. The UK is a world leader in this aspect of science and technology but needs to do a lot more to remain in that position. As far as field testing is concerned, the UK has fallen well behind countries such as the US, Belgium, Canada, France and the Netherlands. Companies who want to invest in biotechnology want to get the genetically modified crops field tested. If the UK industry cannot carry out this work, companies will go elsewhere with their investment.

3. *What future prospects and opportunities does the technology offer?*

Future prospects and opportunities include more control over breeding, incorporation of specific genes to correct specific defects in plants, reduced chemical inputs, more environmentally friendly agriculture, better storage characteristics of the crop, better yield, hybrids, and the use of potatoes to produce novel starches, proteins and pharmaceuticals. Most agronomically important traits are still unknown at the molecular level and derive from a complex set of genes. With the help of molecular techniques these genes can be mapped. This knowledge will allow the development of new strategies for further optimisation of qualitative and quantitative characteristics of potatoes.

Among the non-food uses, there are prospects for high added-value products. Using biotechnological techniques, it is already possible to modify the type of starch produced in tubers and it is perceived that it will become possible to "design" novel starches in this way to meet a wide range of specific uses. "Molecular pharming" of potatoes to produce therapeutic and other pharmaceutical products is also a realistic target, if the desired genes can be expressed in tubers. The potato is a species which is particularly well suited to biotechnological development such as these, in that it is a very high yielding crop, is very amenable to genetic manipulation and its agronomy is very well suited to UK growing conditions.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

The creation of new weeds and disease problems have been suggested as possible risks, but the National Academy of Science states that: There is no evidence that unique hazards exist either in the use of R-DNA techniques or in the transfer of genes between unrelated organisms. The risks associated with the introduction of R-DNA engineered organisms are the same in kind as those associated with the introduction into environment of unmodified organisms and organisms modified by other genetic techniques.

5. *Should biotechnology be regulated by an industry specific regime?*

We do not believe that the industry should regulate itself as such a system would be criticised by consumer and environmental groups. There would be more public acceptance of material released under government regulations. However, it may be appropriate for different industries to have different regimes, according to the issues concerned. For instance, transgenic plants do not raise the ethical issues associated with genetic manipulation of animals.

6. *From a technical point of view is horizontal regulation better than vertical regulation?*

Horizontal regulation represents a more conservative and cautious approach. Vertical regulation is a more logical process, as the nature of the end product is more important than how it was produced, as long as the safety issues can be satisfactorily and confidently evaluated.

The key point, central to your concern on global competitiveness, however, is that the UK is able to operate on an internationally level playing field. The USA has already decided to operate a system based on vertical regulation. Any regulation system which is slower or more demanding than this will clearly put UK-based industry at a disadvantage.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

In some areas there should be no need for a horizontal approach but in others an evolution from horizontal to vertical may be appropriate. Regulations should be based on scientifically established risk and other related factors, rather than theoretical guide lines.

8. *How do current regulations compare with those of other competitor countries?*

- in Europe, we follow France, Belgium and the Netherlands, but harmonisation of national procedures with the EEC should help.
- in the Far East, field releases of GMO's in countries like China are reported to be common. China has extensively grown a potato variety geneticaly modified for higher yields.
- in the USA, the regulations have permitted 134 field tests of genetically modified plants in 1991, as opposed to 18 in the UK.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards:*

(1) Research—Field trials are essential for assessing general performance and the proposed charges for approval in the UK for such work will discourage many.

(2) Product development—Companies will be unable to fully develop their GMO's if regulations are too strict.

(3) Investment—Companies will trial their crops and carry out their research where it is cheapest and least restrictive. eg Strict local regulations on genetic engineering in Basel have influenced large pharmaceutical companies in Switzerland. CIBA Geigy has withdrawn a plan to build a large Biotechnology centre in Basel, preferring to move to France where the political climate is more in favour of Biotechnology and there are fewer bureaucratic obstacles.

(4) Location—US is considered the most preferable at present. Europe has too much opposition from environmental groups particularly in Germany.

(5) Sales and Marketing—a decision from the US Food and Drug Administration in 1992 allows genetically engineered foods to reach the market place. The policy statement made it clear that the standards for federal regulation of new food varieties developed through biotechnology would be the same as they are for any other foods.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

Yes, because we need to maintain an innovative industry with incentives and opportunites for the industry to develop. Regulatory restrictions which discourage industry from fully exploiting the research in this country should be avoided. The Bioindustry Association stated last February (92) that the UK regulation should be clear, practical, user-friendly and technically sound. This is a view with which we would agree.

11. *How best can issues of public acceptance be addressed?*

Public perception can best be addressed by educating and informing the public and by fostering open debate on the issues.

12. *What other factors do we consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

(a) Government and Brussels support for the work on genetic engineering.

(b) Government funding of the basic underpinning science will be crucial to industry's success in the nearer market developments. Fundamental research in plant metabolism and physiology, for instance on starch metabolism and the biosynthetic pathways involved, will enable industry to exploit the opportunities available.

(c) Better public awareness of what genetic engineering is trying to address.

(c) Ethical issues—particularly in the case of animal research.

(d) Intellectual property protection—the main issues being the patenting of life forms animal and plants, genes and gene sequences from animals.

(e) Environmentalists support of the technology.

(f) Labelling regulations on foodstuffs and inconsistency of approach between different countries.

Thank you for the opportunity to comment on this important area of science and technology.

Letter to the Clerk from G P Gent, Processors & Growers Research Organisation

Thank you for your letter of the 19th February inviting evidence on Biotechnology.

Before attempting to pass certain points to you, perhaps I could make some general observations, as follows:

(a) Real "evidence" on this matter is probably not available. We have views and concerns only, on the possible impact of Biotechnology on crop production and environmental issues.

(b) The term Genetically Modified Organism (GMO) is not used in your letter, but the impact of gene transfer is the implied concern in many of the questions.

(c) My comments and observations only apply to plant science and matters in this area must be set against the persistent over-production of temperate foods and political constraints on output.

Now to revert to your list.

1. PGRO exists to support the producers and users of all types of peas and beans (see enclosed brochure) (not circulated). To-date biotechnology has not affected our work directly but the possible introduction of crops that have resistance to "complete" herbicides would have an adverse affect on our crops and most other specialist or horticultural ones.

2. The case for biotechnology and GMO's will, no doubt, be made by companies. Please remember, however, that activity here is for company gain and may be against the public good if it leads to a monopolistic supply situation.

3. For the proponents of this technology, opportunities are boundless, but they must be set against moral issues and the real danger of some techniques affecting the balance of agricultural production.

4. The obvious moral point here concerns animal husbandry, but I will leave this matter to others. The development of crops with resistance to herbicides or to pests or diseases could have far-reaching implications on both farming and environmental matters.

5. No comment.

6. Horizontal regulation is a starting point only and each case must be judged on its own merits.

7. Yes.

8. Biotech companies will cover this point.

9. Regulations affect all the points listed, but at some stage an assessment of non-company factors should be included, with the starting point probably being the question "Do we *really* need the product or technique that is being pursued?" Despite the regular and extremely harrowing accounts of famine in Africa, existing technology can ensure that there is not a shortage of food for the foreseeable future. Output in most developed countries is currently curtailed and real problems usually relate to economic or political factors.

10. No comment.

11 & 12. Public response will probably be based on emotive rather than scientific matters. Indiscreet or biased comments by a high profile politician, or an investigative journalist is likely to have a greater impact on public opinion than statements from people who are perceived as having a visted interest. In my view, GMO's are likely to be viewed as a rather extreme form of plant manipulation that bring risks that are difficult to quantify for products that are often in surplus.

G P Gent

Evidence from the Public Health Laboratory Services (PHLS)

Response to Questions on which Evidence is Invited

1. The PHLS network consists of 52 Area and Regional (A&R) laboratories within England and Wales, the Central Public Health Laboratory (CPHL) and the Communicable Disease Surveillance Centre (CDSC) at Colindale, and the Centre for Applied Microbiology and Research (CAMR) at Porton Down; all of these are coordinated by PHLS Headquarters, also at Colindale. CPHL and the A&R laboratories are involved in the development and application of biotechnology for in-house use in clinical microbiological diagnosis and for the epidemiological typing of pathogenic microbes. When it is necessary or desirable to exploit developments on a larger scale this is generally approached through partnership with a commercial company. Only CAMR has significant involvement in industrial scale biotechnology and much of the evidence which follows relates to CAMR. CAMR is involved in a number of areas of biotechnology, including fermentation, downstream processing, molecular genetics, therapeutic protein and vaccine manufacture, diagnostic enzyme and bacterial protein production. There are also smaller programmes on environmental and industrial applications of biotechnology, for example the use of microorganisms in the detoxification and treatment of waste.

2. Biotechnology is a vital tool in the creation of new products, processes and technological advances which particularly affects the pharmaceutical, agricultural and environmentally based industries, but will also impinge on others. It is particularly important that UK industry continues to support developments in the field of biotechnology. Advances in the field of biotechnology are generally very rapid; if the UK falls behind in this field decline in competitive technology is also likely to be rapid. It is highly unlikely that other developed countries will withdraw from the field, particularly the USA and Japan, and in the medium to long term, this will result in the need for the UK to import the products resulting from such investment. For this reason, it is important for UK technology to be developed and supported through to the market place, or at least through the minefield in protection of intellectual property (for example, by patenting) so that benefits can be derived through licence agreements.

3. Future prospects and opportunities are legion in the field of biotechnology. Traditionally these products tend to be low-volume, high value when compared to manufacturing industry as a whole. Given adequate investment in research, biotechnology has considerable promise in the health-care field, offering the prospect of improved diagnosis, prevention of treatment of both disease and inherited disorders. A greater understanding of genetics may lead to eventual treatments of hereditary disease such as muscular dystrophy,

multiple sclerosis, etc. or even a means of correcting such disorders at a pre-natal stage. In terms of diagnosis, such technology is already being used in the development of rapid methods for the diagnosis of disease and therefore the possibility of both earlier treatment and the limitation of spread of epidemics. Vaccine technology both in the human and veterinary fields has already benefitted from the input of biotechnology and the advantages to both in developing new vaccines and improving yields and productivity of existing products are clear.

4. An area where biotechnology raises issues of safety is the use of recombinant organisms, particularly in instances where release is contemplated. Such studies should continue to be controlled and more support put into research to validate the safety of the release of genetically modified organisms. Environmental release is one such area which has been, relatively speaking, little studied. Vigilance must also be maintained when moving genes from one host to another is contemplated for other purposes, particularly if the intended product is for human use. Accidental release is also a correct concern and some form of control of both research and production facilities is required to minimise risk in this area. The existing UK controls have achieved a wide measure of support from the regulators and the regulated. Informed dialogue coupled with flexibility to adapt regulations as knowledge develops will be a key to maintaining a UK competitive position. In this respect the UK position contrasts very favourably with that of Germany, where the nature and extent of the regulations have all but stifled a developing industry.

5. Biotechnology is a tool to be used by a variety of industries. Thus common elements such as recombinant DNA technology can be addressed, as is now the case, by general controls. On the other hand the particular product of such industries and their use eg vaccines, diagnostics, pesticides, herbicides are likely to need to be addressed on a sector by sector basis.

6. It may be considered that for products intended for human use, horizontal regulation is particularly important, especially where recombinant technology is involved. However, in this instance, vertical regulation is also of importance, as such a product must also be judged by its efficacy and freedom from unwanted characteristics and contaminants. Biotechnological products require their own considerations, which may be different from those applied to other types of products. Quality assurance of recombinant DNA technology derived materials requires control of starting materials, production processes and the final product.

Much of this is beyond the scope of the pharmacopoeia and control must therefore be via the relevant competent regulatory authorities who licence pharmaceutical production. In simple terms vertical regulation alone will not suffice in the present stage of knowledge.

7. Notwithstanding the above (6), a gradual move to vertical regulation may be deemed desirable and possible in certain biotechnology industries, as knowledge develops.

8. Regulations in the fields where CAMR is active, the manufacture of biologically-derived drug products and vaccines (some recombinant) are governed by the relevant regulatory authorities. In the UK the relevant authorities are the Advisory Committee on Genetic Manipulation, the Health & Safety Executive and the Medicines Control Agency (MCA). The requirements of the MCA, which control the end product, are very similar to those of the Food and Drug Administration in the USA and in the Health Protection Board in Canada and the increasingly unified regulations of medicinal products within the EEC. Of more concern however are the disparities in controls of the biotechnological processes which lead to such products and which affect the cost effectiveness of the research, development and production phases. In these aspects European controls are becoming more stringent than those in the USA, or the Far East. The UK thus far has maintained a reasonable balance between effective control and avoiding unnecessary impediments to industrial advances. Again, the contrast between the UK and the German experience in this area should be noted.

9. In terms of competitiveness, the regulatory regime applicable to products at CAMR should oversee the maintenance of very high standards of quality, permitting a competitive edge to be continued. It does, however, lead to high costs in terms of research, development and facilities, and many biotechnological products require years of testing under current regulatory regimes before there is a prospect of a return on investment through the market place. This, in turn, may preclude some industries from setting off on the path to such developments. It is therefore particularly important that any regulatory regime maintains a balance between the need to ensure adequate control and the need to avoid stifling investment in pre-competitive development.

10. The present UK regulatory regime is well suited to maintaining a flexible balance between the need to protect the population and environment from potential risks associated with the technologies, while ensuring that the exploitation of the fruits of scientific research for public benefit is not unduly impeded. Of increasing concern will be the effect of the requirements to impose EEC regulations which it appears may lack the balance and flexibility which have so far characterised the UK approach.

11. Education is required to inform of the benefits which these and other technologies have brought and will bring to the population. There is a tendency in parts of the media and elsewhere to highlight potential and actual risks without making the link to the benefits. Issues of public acceptance can be addressed by a policy

of openness, and a commitment to thorough validation of safety issues before approval to the use of products and processes derived from biotechnology. Fears frequently grow a mixture of ignorance and lack of understanding; measures to overcome these problems will help to alleviate the potential disquiet over the use of such technology.

12. One area which causes particular problems for British biotechnological research is the shortage (comparative to other countries) of centralised funding for pre-competitive research, and support to carry such fundamental research through the necessary development phase to prove to potential customers and/or licensees that commercial exploitation is a viable option and worth investing in. Many good ideas simply do not make it into development phases due to lack of support in the early stages for pre-competitive research and pump-priming exercises. It may be considered appropriate to develop a form of joint exercise between government and industry to meet these aims. There are examples elsewhere where such a arrangement works successfully, for example Braunschweig in Germany, which is funded by both industry and federal government. Similar facilities exist in France through the Centre National de Research Scientifique. In Japan, the Government is actively pursuing the development of links between universities and industry by the establishment of specialised biotechnology centres.

Evidence from the Royal Academy of Engineering

EXECUTIVE SUMMARY

This evidence represents a collation of views from Fellows of The Royal Academy of Engineering, the United Kingdom's independent self-governing body of distinguished professional engineers of all disciplines. The Academy believes that:

- For the benefit of the nation UK biotechnology must be encouraged and supported to capitalise on the existing expertise.
- The potential for creating new products, production and treatment plants, and associated services is great and offers opportunities which must not be squandered.
- The possibility of releasing a non-benign genetically engineered organism into the environment is an important concern. However, to maintain competitiveness the degree of regulation must not be over emphasised. The level of controls introduced in industry should be appropriate to the perceived risk, as applied successfully for many years to such work in laboratories.
- As well as the broad safety regulations pertinent to the process industries, there is a need for sector specific regulations (eg for genetically engineered organisms). However, if the regulations are excessive the anticipated biotechnological revolution may never happen.
- In the pharmaceutical, food and drink industries vertical regulation (based on product characteristics) is preferable to horizontal regulation (based on the manufacturing process). For the control of Red List substances in waste water it can be argued there is a case for the use of horizontal and vertical regulation, depending on the assessment of the degree of risk to which society would be exposed.
- Legislation should evolve as fast as possible from a horizontal to a vertical approach although the need for caution with genetically engineered systems is recognised.
- The extent to which regulations are enforced in competitor countries is believed to give rise to significant disparity even if the regulations themselves are quite similar. Strong regulatory controls at the low risk end of biotechnology are to be avoided if a competitive edge is to be maintained—as has been justified in the USA.
- Research will be carried out in those countries where it is favoured through a less stringent regulatory regime. The economic gain to the favoured country is potentially considerable as it is likely that product development, investment and production will also occur in the country where the research was carried out.
- The exploitation of UK research findings by British companies could be endangered by the present regulatory regime. The danger will be enhanced if legislation moves towards that in force in Germany.
- There is a need for public education programmes dealing with both food safety and the use of biotechnology.
- Funding of university research in this area must continue at a high level but industry cannot be expected to fund it alone. Biotechnology is one important area where academic findings can, through biochemical engineering, be translated rapidly into commercial products.

1. *What is your interest in biotechnology*

1.1 The Royal Academy of Engineering is the United Kingdom's independent self-governing body of professional engineers of all disciplines. The Academy's objectives are the pursuit, encouragement and maintenance of excellence in the whole field of engineering in order to promote the advancement of the science, art and practice of engineering for the benefit of the public. By recognising Britain's most distinguished engineers The Academy aims to take advantage of their wealth of engineering knowledge and experience. The interdisciplinary character of The Academy's membership provides a unique breadth of engineering experience with which to further all forms of engineering.

1.2 This evidence represents a collation of views from Fellows of The Royal Academy of Engineering. It cannot reflect the views of all contributing Fellows nor those of The Academy as a whole. It may, however, be regarded as representative. A list of contributing Fellows and their areas of interest is included at Annex A.

2. *How and why is biotechnology important to UK industry?*

2.1 The UK has strong pharmaceutical, fine chemicals, food and drink industries to which biotechnology applies and which are able to demonstrate a successful track record in the commercialisation of this new technology. These industries are already dependent upon both scientific and engineering advances in biotechnology and will continue to be so in order to remain competitive.

2.2 The UK is second only to the U.S.A. in the number of small biotechnology companies and with a strong biological base these have good prospects. The new market for biopharmaceuticals has been estimated to be between $20–30 billion by the year 2000, representing perhaps some 20 per cent of the overall world market. Additionally, pharmaceuticals is the only manufacturing sector in which the UK market share is growing and is as high as 15 per cent of the world market.

2.3 Biotechnology is recognised by most governments as one of the most important new industrial technologies with the associated processes and products expected to form an increasing proportion of traded goods and services. Its importance is also derived from that part of the market concerned with environmental protection and to ensuring that the individual needs of firms to control their own emissions are met in the most cost-effective manner. UK biotechnology must be encouraged to ensure that the opportunities afforded by the current expertise and favourable world position are not wasted.

2.4 An example of the industrial application of biotechnology is the alcoholic beverage industry. Biotechnology offers the possibility of containing costs through improved yields of high quality crops and through the lowering of production costs by means of enzymes and yeasts, optimised for alcohol and flavour production. Biotechnology has the ability to deliver precise, specific changes in the properties of organisms without introducing unwanted variations.

3. *What future prospects and opportunities does the technology offer?*

3.1 The range of potential new products is vast with genetic engineering having an increasing effect on agriculture and hence the food industry. Also affected will be pharmaceuticals, healthcare products, fine and bulk chemicals together with the capacity to treat toxic wastes. It is estimated that sales of biotechnology-derived products (excluding fermented foods and drinks) will be between 26 and 41 billion ECU by the year 2000. This will depend on the timely introduction of new products at a competitive price in the face of intense competition, principally from the USA and Japan.

3.2 The ability to introduce new properties into brewing raw materials and yeasts offers the prospect of completely novel, more energy efficient, more environmentally friendly processes being developed. This in turn will lead to more cost effective procedures and the availability of a wider range of products to the consumer. There also exists the possibility of spin-off industries arising, based upon brewing technology. Already a UK biotechnology company producing pharmaceutical products has emerged from a major brewing company.

3.3 The estimated required expenditure on pollution control world-wide is at least tens of billions of pounds per annum. Within the UK around £1 billion pa is probably spent on the biological treatment of waste waters and sludges. The opportunities in this area centre on the provision of new plant for extension or replacement of inadequate facilities together with associated planning, design, operating and management services.

3.4 Within the pharmaceutical industry some optimists think that biotechnology will take up to 80 per cent of the pharmaceuticals market by 2010. What is quite clear is that the science base is developing fast and that the pharmaceuticals technology is undergoing a step change. Much is known about the effect of small and large molecules on the human system but only recently has our understanding of biotechnology and modelling really influenced the development of therapeutics. The UK is well placed in new bioscience, but there must be a major question about whether the pharmaceuticals industry, which has been chemist dominated, will be able to cope with the change to a biopharmaceuticals industry.

3.5 Other specific prospects and opportunities include:

- Synthesis of effect chemicals with highly specific biological effects (eg antibodies, enzymes, pheromones);
- Bioremediation (eg of wastes, soil and contaminated land);
- Improved agricultural practices (eg genetically modified plants, mycorhizal cultures, non-pesticide means of pest control);
- Therapeutic and clinical diagnostic techniques;
- New approaches to chemical purification (eg affinity separation);
- Forensic uses (eg detection of steroids and other growth promoters, genome typing).

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

4.1 It is first necessary to make the distinction between employee safety and public safety. Practices to ensure employee safety need not differ from those existing in, for example, the food and process industries. With regard to public safety there is some concern that the safety issue has been overstated. The chemicals produced and used by the biotechnology industries are no more hazardous than many chemicals already in common use, e.g. as pesticides. Therapeutic agents are subject to the normal procedures used in the medical industry and are therefore not a new problem. The principal concern is the capacity to create whole organisms, (both micro- and macro-), using genetic engineering and the possibilities that any subsequent release of such organisms into the environment might not necessary be benign.

4.2 The degree of regulation introduced must be appropriate to the associated risk. Excessive regulation will yield no return on the investment and will harm the UK competitive position. An example of this is the brewing and alcoholic beverages industries where the application of the same strict controls at all levels of risk seem particularly inappropriate where only organisms which present insignificant risks will ever be employed. The concept that not all recombitant organisms possess the same degree of risk has been applied successfully for many years to such work in laboratories and such a philosophy should be adopted for large scale commercial processes.

5. *Should biotechnology be regulated by an industry specific regime?*

5.1 Regulation and safety is extremely important but by continuing down the existing path the products of biotechnology may become excessively expensive and the potential boon promised from biotechnology will not materialise. Many of the reasons for the slow commercialisation of biotechnology are right and proper but there is a need for further careful consideration. The problem should be addressed by a group of highly informed engineers (biochemical and perhaps mechanical), biological and social scientists, businessmen and responsible politicians.

5.2 Many features and operations in the biological industries which demand overall regulation are already controlled through the broad safety regulations of the process industries, e.g. the design codes of practice and emission and environmental standards. However, the criteria for safe and effective products require sector specific regulations e.g. to cover genetically engineered organisms.

5.3 Once organisms have left the early experimental stage and are approaching commercial exploitation, they should be regulated on an industry basis rather than by method of production. In the case of alcoholic beverages, the acceptability of a new production process should be assessed by the Advisory Committee on Novel Foods and Processes of MAFF. Clearly the use of new biotechnological methods should be considered as part of their deliberations. The separation of biotechnological methods from all other 'novel' processes and their assessment by a completely different procedure seems inappropriate.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

6.1 It appears that the answer to this question depends on the industrial sector although the view has been expressed that it is doubtful whether more legislation is needed. Given that biological products are often not single molecular species, the US Food and Drug Administration regulations require a definition of the processes. Ideally a product should not have to bear any particular label on the process but nevertheless at a technical level it should be regulated.

6.2 In the food and drink industry regulation is often on the process but it can be argued that the nutritional status and safety of the product as consumed is of far greater significance than the process by which it was made. Thus technically, vertical regulation is clearly preferable to horizontal regulation. The current situation where a mixture of both types of regulation exist is the worst possible situation.

6.3 For pharmaceuticals it is vital that regulation should be vertical if innovative processing developments are not to be stifled.

6.4 Taking as a parallel the requirement to use BATNEEC for control of Red List substances in waste waters and also to meet NRA/EC emission and environmental standards, it can be argued that there is a case for the use of both horizontal and vertical regulation, depending on the assessment of the degree of risk involved, especially where precise knowledge of likely impacts is lacking. It is thought desirable to exercise judgement as to which approach might be best according to the strength of knowledge about the risks to which society would be explosed.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

7.1 Legislation should evolve as fast as possible from a horizontal to a vertical approach as experience accumulates making it possible to focus on the product, especially on genetically engineered systems. Presumably this will involve changes at the European level since much current legislation in the biotechnological field has its origins in EC Directives.

7.2 In the particular area of genetically engineered organisms it is recognised that establishing reliable tests to preclude adverse effects resulting from the escape of engineered organisms to the environment has obvious difficulties. Possibly it would be expedient to require all emissions from plants using such organisms to be disinfected (eg chlorinated), a form of horizontal regulation, or rendered sterile as judged for example by a zero plate count, a form of vertical regulation.

8. *How do current regulations compare with those of other competitor countries*

— in Europe
— in the Far East
— the USA?

8.1 As far as emission and environmental standards for conventionally measured parameters are concerned the regulations in virtually all the developed and many developing countries are now quite similar. The differences, such as they are, often manifest themselves more in terms of the extent to which the regulations are enforced.

8.2 With regard to genetic engineering regulations there are significant differences worldwide. The regulations in continental Europe tend to be more severe than in the UK. For example, in Germany the regulations have become so restrictive as to prevent laboratory work other than with simple commonplace micro-organisms, whereas in the USA they are becoming more modest and in Japan there seems to be little awareness of a need.

8.3 The USA has taken a lead in rejecting the need for strong regulatory control at the low-risk end of biotechnology so that resources can be concentrated where they are most needed in procedures which potentially involve high levels of risk. This has been justified on the grounds of maintaining the competitive edge that the USA already enjoys in the field of biotechnology. This is clearly a matter that should concern all those involved with UK biotechnology. Whilst other EC countries are having to work under broadly similar biotechnology legislation to the UK the detail does differ markedly. In particular, the costs of obtaining a deliberate release consent vary from country to country, no charges at all being levied in France and Belgium compared with charges of the order of £2,000 in the UK.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards*

(1) research
(2) product development
(3) investment
(4) location
(5) sales and marketing?

9.1 The competitiveness of the EC in general and of the UK in particular will be affected by the apparently stricter regime of regulation in one country compared to another. Already research by multinational companies has moved from Europe to the USA to avoid harsh regulations, and even within Europe some countries are favoured for release experiments. Long term it is likely that product development, investment and production will take place in the country in which the initial research was carried out. Thus the gain to the economy of the favoured country will be considerable.

9.2 It is postulated that the more severe the regulatory regine the more likely are those regulated to have technology more advanced than in less regulated countries and thus potentially more saleable when the latter begin to seek improvement. On the other hand, if the regulatory regime increases costs of production then those more severely regulated may well find it difficult to compete with those less constrained—the nowadays familiar problem of securing a "level playing field".

9.3 A recent Green Paper on the release of genetically engineered organisms gives rise to a concern that the burden of proof—and its cost—is being transferred to university groups. This is especially serious for process engineering groups concerned with scale-up.

9.4 In the area of pollution control it is doubtful whether UK competitiveness in the five activities identified is much distorted by the regulatory regimes in other developed countries. Within the drinks industry it is conceivable that switches of production to welcoming countries could occur in the future as the industry becomes increasingly international.

10. *Is there a danger that the present regulatory regime will prevent the exploitaiton by British industry of research conducted in the UK science base?*

10.1 As indicated in the previous answer there is a danger that the present regulatory regime could prevent the exploitation of UK research findings by British Companies. This is particularly so if the regulations move in the direction of German legislation.

11. *How best can issues of public acceptance be addressed?*

11.1 As a general statement, we all have to make a considerable effort to educate the public. This is well recognised by the Research Councils and DTI who co-ordinate their activities in the Biotechnology Joint Advisory Board.

11.2 With regard to genetic engineering applications, the issue of the deliberate release of engineered micro-organisms and whole plants needs to be very carefully debated. Unless there is very strong evidence and opinion to the contrary, engineered organisms must continue to be strictly contained. A definitive report from the proposed environment Agency taking account of medical opinion plus that of other relevant interests (eg, agriculture and fisheries should be disseminated to the public through the media if or when public anxiety becomes manifest.

11.3 Within the food and drink industry the question of public acceptance is a major concern. Currently it is thought that public opinion is largely hostile to the idea of consuming products made with genetically-engineered raw materials. This has come about in a number of ways. Recent food scares have not, in general, increased trust in public bodies of food companies. This needs to be addressed by public education programmes dealing with both food safety and the use of biotechnology. This will require effort on the part of both Government and industry. The proposals for regulating the use of genetically-modified organisms and for the labelling of foods produced with them only leads to increased consumer concern regarding product consumption. This will undoubtedly be a significant obstacle to the application of recombinant DNA technology in the alcoholic beverage industry.

11.4 In environmental matters generally there are numerous channels allowing the public to receive information and influence decisions. There is ready access to authoritative independent bodies and "watch dogs" of various kinds (to be supplemented by a new Environment Agency).

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

12.1 Biotechnology is one of the few areas where academic findings are translated rapidly into commercial products. To permit this to continue it is essential that funding of university research in this area continues at a high level. It is not sufficient to expect industry to fund this research. Most of the techniques which now form the cornerstones of industrial biotechnology were orginally developed in academic departments with no thought for future commercial uses. Biochemical engineering is concerned with the development and operation of biological production methods, central to translating, in the shortest time possible, the discoveries of biotechnology into commercial products through processes which are safe, reliable, economic and environmentally acceptable.

12.2 The strength of the R&D effort is certainly important in the medium and longer term but, as in the water industry, the concentration of research in private hands makes it difficult to assess the extent of progress given commercial confidentiality. It is suspected that the bias towards short-term requirements and increasing fragmentation among bodies with not particularly impressive track records in R&D may be becoming excessive.

12.3 There is a need to build up small ventures. In the recent past, the largest UK biotechnology venture fund was forced to invest in the USA because of the lack of linkage between good bioscience and good small company capabilities in the UK. This could be changed by the DTI but it woud require an injection of people with small company experience as advisers.

12.4 The importance of regulation and safety is recognised but many small venture capital companies based on biotechnology often collapse because of the cost of, firstly, getting facilities built and equipment installed and validated; and secondly, production routes approved. The time required to obtain regulatory approval of plant and product after completion of the basic research may be as much as 10 years and often has little to do with science or engineering. The sensible resolution of these regulatory problems is vital for our economy. If these matters are over emphasised, it is certain that other parts of the world will continue developments in the area; and many will err substantially on the wrong side, throwing caution to the winds, and producing much cheaper but unsafe products.

12.5 In the production of healthcare products, the precise manufacturing route has to be established in the form of a written protocol which must be exactly followed in order to guarantee quality. This requirement is totally contrary to the normal way by which multi-step production processes are improved, whether by increased throughput or product quality. Usually, the rate-limiting step of bottleneck can be worked upon research (science or engineering) and when improvements have been achieved, they can be introduced into the plant. However, with healthcare products, the whole production process may have to be revalidated. The requirement is a great inhibition to innovation and improvement. Careful consideration should be given to a more sensible "modus operandi" for improving processes whilst maintaining quality control.

ANNEX A

Contributors to the evidence

Professor B Atkinson FEng

Director-General of BRF International, a research organisation concerned with the alcoholic beverage, malting and allied industries, with experience in recombinant DNA methodolgies as applied to brewing yeasts.

Professor R Clift FEng

Professor of Environmental Technology, University of Surrey. An Executive Director of a company concerned with "downstream processing" of biologically active species.

Chairman of the AFRC/SERC Clean Technology Unit which has interests in using biotechnology for clean synthesis and in bioremediation.

Mr P J Davidson FEng

Responsible for Process Engineering in the Engineering function of ICI, which until recently involved some contact with the issues of manufacturing Biopharmaceuticals and Bioproducts.

Dr A L Downing FEng.

Interests in the application biological processes for the treatment of water, waste waters and sludges; and quantification of biological processes including the assimilative capacity of the environment.

Professor P Dunnill FEng

Professor of Biochemical Engineering, University College London. Director of the SERC Interdisciplinary Research Centre for Biochemical Engineering.

Professor M D Lilly FEng FRS

Professor of Biochemical Engineering at University College London, a Director of the International Institute of Biotechnology, and Past Chairman of the International Organisation for Biotechnology and Bioengineering.

Professor A W Nienow FEng

Rhone-Poulenc Professor of Biochemical Engineering, University of Birmingham. Director of the SERC Centre for Biochemical Engineering at the University of Birmingham. Committee member of the SERC Biotechnology Directorate and a member of the management committee of the SERC/DTI LINK in Biochemical Engineering. Formerly a Council Member of the AFRC and Chairman of its Engineering Advisory Group.

Evidence from the Royal Agricultural Society of England

1. *What is your interest in Biotechnology?*

1.1 One of the principal purposes for which the Royal Agricultural Society of England was founded in 1838 was to promote the application of science and the dissemination of scientific knowledge to the agricultural industry, and the transfer of appropriate technologies to farming. The Society's interest is, therefore, both that of an organisation concerned with the technological advance of agriculture and, reflecting its membership, that of the enlightened farmer who will assess and, where appropriate, adopt the technologies emerging from bioscience.

1.2 The competence of the Society lies in the field of agriculture and, therefore, the comments which follow will be restricted to that field of application.

2. *How and why is biotechnology important to UK industry?*

2.1 UK agriculture is a knowledge based industry and in particular relies heavily for its competitive edge on scientific application in both production and other sectors of the food chain.

2.2 The development and application of biotechnical advances is important to UK agriculture for the following reasons:

- (i) First, because they offer the opportunity to stay at the leading edge of progress and competitiveness through the promise of improved productivity and the introduction of novel crops and products for the mature and sophisticated European and Atlantic markets as well as offering opportunities in global markets.
- (ii) Second, because investment in the United Kingdom in successful biotechnologies for agriculture globally will be necessary to maintain in the UK the intellectual capacity represented by the science base which underpins a modern agriculture and food industry.
- (iii) Third, because successful investments in biotechnology will enable the UK to capitalise on one of its strengths (bioscience) in global terms and remain an important participant in what will undoubtedly become a growth industry worldwide.

2.3 From the consultations which the Society has held as part of its own international programme it is clear that, worldwide, farmers, agriculturalists and scientists face twin challenges. First, to continue to extend the means by which an expanding population can be fed and, second, to do so by means which are increasingly benign to the natural environment.

2.4 Biotechnology has a vitally important role to play in meeting these challenges and at the same time can offer hope of improving the sustainability of the agronomic systems employed. The rewards to these countries which can develop and market successful systems and products will be immense.

3. *What future prospect does the technology offer?*

3.1 In broad terms the answer to this question is that these technologies will be mainstream in the development of more sustainable agricultural systems. It may be more helpful, however, to provide examples of the opportunities offered by biotechnology in the pursuit of this goal rather than merely proffer a general view.

3.2 In farm animals:

- (i) to improve efficiency and productivity by more accurate selection processes in breeding eg, through sex choice;
- (ii) improvements to the utilisation of food especially in the ruminant;
- (iii) the transfer of desirable genes across species barriers opens the way to the possibility of introducing to species which do not have the genes for resistance to disease;
- (iv) improved vaccines and other health products will strengthen further the armoury of prevention;
- (v) improvements to the quality of animal fats to meet changing dietary needs.

3.3 In crop plants:

- (i) to improve resistance of plants to pests and diseases;
- (ii) to manipulate the chemistry of plants so as to tailor them more specifically to a range of food and industrial uses;
- (iii) to amend the tolerance of plants to withstand a wider range of climatic and other environmental factors so that the range of useful plants can be safely extended;
- (iv) in the longer term improvement to the efficiency of photosynthesis may be possible as may the transfer of nitrogen fixing properties to crop species which do not now possess them;
- (v) diagnostic techniques to improve the efficiency of current breeding methods.

3.4 The engineering of micro-organisms to provide crop protection products is already established technology as are some biological control methods of crop protection especially in protected situations; fermentation technologies offer the opportunity of industrialising the production of some foods. Other work is of importance in the development of bio-fuels.

3.5 In all of these ways, in others not referred to in this brief selection of examples and in others not yet envisaged, biotechnologies will contribute to the sustainable exploitation of renewable resources.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

4.1 Safety issues arise particularly in relation to the genetic modification of micro-organisms, plants and animals, especially where such modified organisms have the ability to self-replicate. For example, concerns are expressed that new forms of pathogen may emerge, or that in the process of gene transfer in animals, the animal/animal or human/animal disease interface may be altered and new epidemics or new zoonoses may appear. Other concerns relate to possible risks to food safety, or that altering the herbicide tolerance of plants to provide more effective weed control, may result in changes to the established orders of species competitiveness and so on.

4.2 Safety issues are best addressed by some form of regulatory body which is science based and supported by an authority which has the power to enforce the system. From the standpoint of the customer for and user of the products of biotechnology there is great merit in a process which adapts, wherever possible, existing legislation which is familiar and understood. The Advisory Committee system has stood the test of time in the United Kingdom. The Control of Substances Hazardous to Health is an example of the kind of legislation to which we refer.

4.3 We are aware that in the United States regulation is through the adaptation of existing legislation and this has not only the benefits we suggest above but also avoids introducing another regulatory body with possibly conflicting bureaucratic interventions. It is a matter of some concern to the Society that a number of the science based companies which are our customers have expressed concern to us that the EC Directives 90/219 and 90/220 have done little to encourage research and development or, indeed, improve public understanding and confidence.

4.4 It is vital that the public—consumers and customers—both understand and have confidence in the systems and especially the way in which risk assessment procedures are worked out, applied and reviewed. It is important too that informed lay opinion is involved. Whether this objective is best met by involvement of lay interests on a representative basis is a matter for consideration. Whatever the system, the fruits of biotechnology will not be harvested and, therefore, the investment in research and development will not be maintained if customers do not buy the products and, in turn, if consumers do not share that confidence.

5.–10. *Questions dealing with the regulation of biotechnology, the comparison of regulatory measures in the UK with those of other countries and the effect that measures may have on competitiveness.*

5.1 The Royal Agricultural Society has no vested interest in the regulation of biotechnology. Its concern is with the use of the products of biotechnology and to ensure that those products which will ensure a safe and competitive industry are available to UK agriculture.

5.2 A number of industries are developing biotechnologies and applications appropriate to them and there is, in consequence, no biotechnology industry as such. It follows, therefore, that the different products of biotechnology will require separate evaluation.

5.3 It seems important to us that a credible regulatory framework must make clear to industry interests, to scientists and to consumers, where authority and accountability lies, what is necessary to obtain regulatory decisions and that the authority to accept or reject will work. Clearly too the regulatory mechanism must be adequately resourced for the task if it is to operate in a timely way and avoid slowing down the rate at which products can be approved.

5.4 Agriculture is an international business and the servicing of its needs has long been international too. If the regulatory system in a country is more expensive, more restrictive or more prolonged than in another then this will materially affect both rate and volume of investment in developing biotechnology in that country. This applies particularly to a country like Britain where its own agriculture base, although of high quality, is relatively small in terms of a market when looked at from a global perspective. It is important, therefore, that companies upstream of the farm gate have a framework which does not undermine competitiveness in world markets—for exports are vital, just as they are vital to the future of the UK agricultural industry itself. If follows that, despite the quality of the basic science base in the UK, the investment to develop and apply the technologies may flow to other countries if the regulatory framework is restrictive relative to those of competitor countries. This would be detrimental to the UK's trading position and lead to further decline in UK manufacturing industry and agriculture and, no doubt, to further erosion of the UK public sector science base on the basis that industry has failed to capitalise on the discoveries and advances of the scientific community.

5.5 In so far as users are concerned it is the characteristics of the product which are important. Therefore, there are strong grounds to favour vertical regulation. However, horizontal regulation may be appropriate, normally in the early stages of evaluation, where the process by which the product is derived raises safety concerns.

5.6 Much of the debate which is taking place about biotechnology and many of the concerns which the Society has encountered relate not to safety, however, but to the ethical aspects of some of the techniques and applications of biotechnology. A regulatory process concerned with efficacy and safety is unlikely to be a satisfactory mechanism if it is to become a forum for debates about ethical issues or issues which have more to do with the changing structure of farming than safety. It is important and necessary, therefore, that some other recognised open but structured forum develops for debates on these issues.

11. *How best can issues of public acceptance be addressed?*

11.1 This is a matter of immense importance to many industry sectors and not least to agriculture. We have already suggested that one of the problems faced by agriculture is that the debate about biotechnology is a complex one involving social, cultural, ethical and environmental issues as well as scientific, technical and economic imperatives. There is a widespread feeling that the debate about biotechnological issues is swayed by the media attention paid to the extreme pressure groups and that there is an urgent need to explain to society at large what biotechnology is about.

11.2 At the moment the debate is handled in an unstructured way with no real coordination or focus, and yet the topic is one of the most important facing society. The Royal Society, the British Association for the Advancement of Science, the Institute of Biology, the Science Museum and the RASE are but a few of the bodies who have mounted meetings conferences or displays appropriate to the debate. However, it is doubtful whether un-coordinated activity of this nature is the most effective way of managing a debate of the importance which should be attached to that about biotechnology.

11.3 The attention of the Committee is drawn to an approach adopted in the United States by a number of Universities and Research Institutes in 1988–89 where some six such organisations came together to form a National Agricultural Biotechnology Council (NABC) with the following objectives:

(i) Provide an open forum for persons with different interests and concerns to come together to speak, to listen, to learn and to participate in meaningful dialogue and evaluation of the potential impacts of agricultural biotechnology;

(ii) Define issues and public policy options related to biotechnology in the food, agricultural and environmental areas;

(iii) Promote increased understanding of the scientific, economic legislative and social issues associated with agricultural biotechnology by compiling and disseminating information to interested people;

(iv) Facilitate active communication among researchers, administrators, policy makers, practitioners and other concerned people to insure that all viewpoints contribute to the safe and efficacious development of biotechnology for the benefit of society;

(v) Sponsor meetings and workshops and publish and distribute reports that provide a foundation for addressing issues.

11.4 From the original six institutions the consortium which constitutes the Council has grown to 13, and the reports of the annual conferences, of which there have been four to date, form a reservoir of useful and pertinent information available to all interested parties, whether in the United States or overseas, for a modest subscription. A small administrative and editorial staff is funded by a private foundation and the USDA.

11.5 European agriculture and indeed United Kingdom agriculture is rich in associations of one kind or another and there are many who would argue that there is no need for another. However, if can also be argued that there is a need for a more coordinated and effective effort than at present exists if society is to come to views based on knowledge rather than, as so often happens, the dissemination of information by lobby groups and others which often constitutes little more than beliefs masquerading as fact. Not all models transfer comfortably from the United States to the United Kingdom but that of the NABC deserves close and careful evaluation.

11.6 The RASE is at present engaged in an attempt to establish a Unit at the National Agricultural Centre to provide a source of factual and unbiased information about agriculture to the general public. This in itself is no easy task. However, the Society would be willing to play its part, within the limits of its resources, to bring into being an NABC-like consortium in partnership with others. It is clearly important for science and industry to debate the issues involved with interested parties on an open but informed basis, and not least in language intelligible to the general public. If this can be achieved in the United States of America it can surely be possible in the United Kingdom.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

12.1 Reference has already been made to the importance of basic research and the purpose of repetition here is simply to underline the need for public sector funding to ensure not only an adequate research capability which can attract funds from community programmes and the private sector, but also to attract, educate, train and retain the necessary quality of human resources.

12.2 Reference must be made too to the matter of intellectual property rights. Intellectual property rights are important in the case of say, pharmaceutical products and living organisms and these in turn are the substance of biotechnology in agriculture. It would appear that, as in the United States, the European Patent Office grants very broad claims to inventors. The broad claim approach is perhaps best illustrated by the case of the "Harvard Mouse" in the US which in effect claims any transgenic non-human mammal a patent, presumably granted by examiners who at the time had no basis for denying the claim.

12.3 If the motive behind intellectual property rights is the benefit which arises to society by the bringing forth of an invention at least cost to society, rather than simply equity to the inventor, then society is acting logically in granting the smallest degree of protection needed to induce the invention. In this context it can be seen that the granting of broad patents can be a cause of uncertainty and thus disincentive to invest by others. The degree of protection needed in agriculture requires particularly fine consideration, especially in the case of applications such as seeds where the returns to plant breeders are affected by the saving of home grown seed by farmers.

12.4 In conclusion, it must be said that, if biotechnology is to advance, it requires investment and, without some certainty of appropriate protection, the investment is unlikely to be forthcoming. Put most simply, companies and organisations in this field will no doubt invest in those countries where the framework is most supportive, all other things being equal.

12.5 The Society shares the view that it is important to the future of the United Kingdom that this country attracts and retains the investment in biotechnology necessary to ensure the scale of activity and successful application which will allow Britain to reap its share of reward from this growth area for the 21st Century.

Evidence from the Royal Botanic Gardens, Kew

The Royal Botanic Gardens, Kew maintains the world's most significant collections of living and preserved plants. The main thrusts of its research are concerned with:—

1. *Systematics and Evolution*

Accurate naming and rapid identification of species; determining species origins and relationships

2. *Conservation*

Preserving biodiversity both *in situ* and *ex situ;* species survival and re-introduction

3. *Economic Botany*

Ethnobotany and the known uses of plants; identifying novel uses for plants

Questions have been answered that relate to Kew in the context of our activities. Questions left unanswered currently do not apply in a Kew context.

Question 1—What is your interest in biotechnology

The Royal Botanic Gardens, Kew (RGB, Kew) is not primarily concerned with biotechnology business. However, its mission statement and legal responsibilities make it important that RBG, Kew uses established biological technologies to fulfil its declared and allotted roles, and where necessary develop novel techniques to solve specific problems or in response to changing circumstances. The availability of its plant materials (living and dead), research information, and the transfer of its advances in biotechnology practice are important factors nationally and internationally, and certainly contribute to Britain's competitive edge both in science and technology.

Two major uses of biotechnology at Kew are:—

i Micropropagation

The principal objective is the micropropagation of plants from tissue. This is of importance for particular endangered species which are difficult to propagate by conventional means, In addition, *in-vitro* seed germination is carried out including the dual culture of orchids and fungi. Experiments are under way which will evaluate the long term storage of plant material by cryopreservation techniques.

ii Seed Conservation

This involves selective targeting of seed for collecting from native habitats. The long term storage of seed requires technology involving strict control of low temperature regimes (including cryopreservation) and controlled levels of desiccation. These genetic resources are part of Kew's conservation programme. However, international agreements such as the Biodiversity Convention in Rio will affect the question of who owns the genetic material in the future and how profits from their commercial exploitation are fed back to countries of origin.

Other uses of biotechnology at Kew include:—

(i) Biological Interactions—Biological control plays a major role in reducing the use of pesticides and thereby reflects an environmentally-friendly stance on such issues. We aim to identify plant metabolites that modify insect development that could be transferred to crop plants to enhance their resistance to herbivory.

(ii) Molecular Systematics—Polymerase chain reaction (gene amplification techniques)—DNA sequencing

(iii) Anatomy—orchid-fungus symbiosis

(iv) Cytogenetics—*in situ* hybridisation (dot blots, chromosome painting)—genetic fingerprinting

(v) Biochemistry—extraction and evaluation of biologically active compounds

A part of Kew's mission is to facilitate the building of local capacity in developing countries. If this involves the transfer of technology, it will be accomplished using current best practice and in compliance with industrial safety standards.

Question 2—How and why is biotechnology important to UK industry?

It is important to UK Agriculture and Horticulture that Kew identifies and maintains biological diversity and thereby rapid access to gene pools of native and exotic species. This has already led to considerable collaboration with overseas governments, the pharmaceutical industry and the development of biotechnological techniques for use in evaluating the role of plants in plant-animal interactions eg taste hormone receptors that are affected by plant compounds.

Question 3—What future prospects and opportunities does the technology offer?

(i) Increased efficiency in identification of species and indicating their relationships.

(ii) Increased efficiency and cost-effectiveness in promoting the survival of species (retaining biological diversity).

(iii) Genetic engineering allows the transfer of useful DNA between widely unrelated organisms. However, beneficial exploitation using this technology will be reduced if the pool of genetic variation available from plants is restricted either temporarily (eg by legislation) or permanently (eg by extinction).

Question 4—Which developments in biotechnology raise issues of safety and how should they be addressed?

Currently this appears not to apply at Kew except where gene cloning is used for making templates for DNA sequencing reactions through a bacterium. The risk is relatively low and is covered by tried and tested procedures.

Question 5—Should biotechnology be regulated by an industry specific regime?

No—this area is covered by safe working practice under COSHH or similar safety legislation.

Question 9—What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards (1) research?

Any regulation which is costly and must be closely monitored may promote competitive disadvantage.

Question 11—How best can issues of public acceptance be addressed?

(i) To inform the public of the ethical and moral implications of the application of biotechnology and encourage wide debate in society eg improving public understanding through COPUS (The Committee on the Public Understanding of Science) and popular scientific articles.

(ii) Public acceptance of biotechnology depends upon no over-exaggeration of risk.

(iii) Issues in question 3 ii will impinge on public acceptance both with regard to conservation success and to the public purse.

Caveat to the submission

The definition of biotechnology used in the submission has been based on the description of biotechnology in the executive summary of the ABRC Biotechnology sub-committee report and is therefore very broad. The definition of biotechnology could be narrowed to the introduction of genetic material from one species of organism into another such that the genetic material is stably integrated into the recipient organism and then can be expressed. The purpose of biotechnology in this context is the production of new traits or compounds different from those expressed in the native organism. Such a definition would currently eliminate all technologies used at Kew and included in this submission.

Evidence from the Royal College of Veterinary Surgeons

EXECUTIVE SUMMARY

The Royal College of Veterinary Surgeons (RCVS), under the Veterinary Surgeons Act 1966, has responsibility for maintaining standards of veterinary care through education and professional guidance. Its interests in relation to biotechnology relate, thus, to ensuring a sound veterinary education and research base for the advancement of knowledge of animal disease, its prevention and control. However, of equal importance is the role of the RCVS in safe-guarding the welfare of animals involved in biotechnology research, and in its application in agricultural and other industries. Finally, the potential impact of animal related biotechnology on our environment, and the involvement of animals in the advancement of human health care through these technologicla advances, are of concern to members of the RCVS.

Our major concerns relate to the mechanism of control, decision making and public perception of these aspects of biotechnology to ensure the technological advances are best harnessed whilst animal welfare is not prejudiced.

We recommend that a single all-embracing body should be responsible for ensuring that decisions relating to the use of biotechnology in animals both in research and its industrial application are taken with due regard to animal welfare and the public interest. Furthermore, that this body should have a remit to improve public understanding of the potential benefits of biotechnology.

Responses to Questions on which Evidence has been Invited

Question 1.

What is your interest in biotechnology?

The Royal College of Veterinary Surgeons (RCVS) was established by Royal Charter in 1844. Its statutory responsibilities as defined in the preamble to the Veterinary Surgeons Act 1966 are "to provide for the management of the veterinary profession, for the registration of veterinary surgeons and veterinary practitioners, for regulating their professional education and professional conduct and for cancelling or suspending registration in cases of misconduct; and for connected purposes".

It will be clear, therefore, that the RCVS has a strong interest in all aspects of biotechnology which relate to animal production, and the treatment of disease. Also in ensuring the inclusion of biotechnology as an essential component of veterinary research base to ensure the appropriate application of biotechnology in the advancement of our understanding of the prevention and treatment of animal disease.

Finally, it should be recognised that under the Animals (Scientific Procedures) Act 1986, veterinary surgeons are required to provide advice on the health and welfare of animals used in research, including novel applications of biotechnology. Hence the verterinary profession makes its contribution to the application of biotechnology in the understanding and better treatment of human as well as animal disease.

Questions 2 & 3.

How and why is biotechnology important to UK industry?

What future prospects and opportunities does the technology offer?

There are five main areas in which animal biotechnology is currently being applied and which will be significant in future development and application of this technology.

(a) To provide a better understanding of animal disease and improve our diagnostic capability. For example, the production of diagnostic agents such as monoclonal antibodies, DNA probes and the application of polymerase chain reactions (PCR) will enable us to detect minute quantities of infective material and genetic abnormalities before clinical signs have become apparent. This will have a major impact on the improvement of diagnosis of disease.

(b) To improve our understanding of human disease, particularly through the use of genetically manipulated animals as models of such disease. Thus, as our understaning of the genetic component of human disease increases, so we may be able to introduce the genes responsible for aspects of such disease into animals thus providing highly specific models of those diseases, eg the recently discovered mouse model for cystic fibrosis.

(c) To develop better models of treatment of disease through improved therapeutic agents, and prevention of disease through new vaccines. For example, the genetic modification of micro-organisms to design new medicines, such as antibiotics which overcome bacterial resistance, may lead to the development of specific agents effective in the treatment of bacterial, parasitic, fungal and viral diseases. Through the use of recombinant DNA technology, vaccines based upon antigenic sub-units of the infectious organisms can be economically produced which have the promise to be both immunogenically more effective and safer than traditional vaccines.

(d) To improve agricultural and other livestock by various methods of speeding up the supply of desirable genomes, for example by embryo transfer and sex determination methodologies.

(e) To aid the production of safe food for human consumption through the reduction of levels of infection and diminishing the reliance on prophylactic medication in feed. In particular, the development of disease resistant animal strains offers great potential for benefit to human safety.

Many of the fundamental techniques of biotechnology, such as transgenesis, will have a major impact in all of these areas. However, current methods of producing transgenic animals are difficult to execute. More work is required both to identify the useful genes and regulatory DNA sequences and to determine the optional conditions for their introduction and expression. Such studies will also provide insights into the regulation of gene expression for the improvement not only of animal efficiency but also enhance resistance to disease thus improving animal health and welfare. For example, the development of Salmonella resistant strains of poultry will have major economic, health and welfare benefits.

Finally, methods are well developed to map the human genome which will enable the localisation of genes on identified chromosomes and linkage analysis to determine whether individual loci are on the same chromosome. Similar methods are being developed to map the genomes of animals, particularly cattle, pigs, chickens and mice, and whilst our present knowledge is far behind that of human genome, the gap is rapidly narrowing.

Questions 4 to 10 inclusive.

Clearly, the RCVS has an interest in encouraging animal-related biotechnology and its application in veterinary research through the development of a competitive scientific and industrial environment with effective transfer of technology and knowledge between academia and industry. We would support moves to improve this situation. However, the specific points raised in questions 4 to 10 in relation to regulations and competitiveness do not fall within the remit of the RCVS except in situations where the competitive use of biotechnology may compromise animal welfare.

Question 11.

How Best Can Issues of Public Acceptance be Addressed?

In addressing this question, it is important to understand not only the wide range of areas in which public disquiet exists in relation to animal biotechnology, but also the depth of misunderstanding upon which much of that disquiet is based. In broad terms, areas of perceived public concern fall into three categories; animal welfare, human safety and environmental hazards. From the foregoing, it will be clear that the RCVS has concerns in all three areas.

It will be further apparent that animal biotechnology has application in two major fields; biomedical research (including diagnosis and control both of animal and human disease) and agricultural production. Public disquiet in both of these fields is very real and probably arises from a lack of general understanding of the issues involved which signals the need for greater communication of the enormous potential benefits of biotechnology. In the absence of such communication, the public is highly susceptible to the emotive arguments of the extreme fringe which, for various reasons, would seek an end to the application of biotechnology in animals.

Alongside this lack of communication, there is an equal concern about the mechanisms by which ethical decisions in relation to animal biotechnology are reached. One might argue that adequate structures already exist to manage such ethical decisions in each of the major fields mentioned above. For example, the Animals (Scientific Procedures) Act 1986 provides a structure for determining justification of research projects and procedures prior to the research being performed. At its highest level, the Home Secretary has an appointed Animal Procedures Committee to advise on such ethical decisions. Likewise in the field of agriculture, the Farm Animal Welfare Council advises the Minister on aspects of concern in agricultural practice which might include those associated with animal biotechnology. At a third level, the RCVS, acting as an independent professional body, provides ethical guidance to the veterinary profession on matters of professional and ethical concern. Such guidance has recently included various aspects of animal biotechnology, for example the performance of embryo transfer in agricultural practice.

Nevertheless, each of these bodies (and perhaps several others pertinent to this ethical debate) is working independently of the others. Decisions taken with regard to justification of research proposals may have long-term, downstream implications with regard to what will become standard agricultural practice in the future. Furthermore, developments occur on an international basis such that effective domestic regulation may not be sufficient to avoid importation of welfare problems. Both animals and the technology applied to them move from one field to the other, from research to application, often creating significant ethical dilemmas for the veterinarians concerned. Furthermore, the veterinary profession stands in a unique position of both public trust and scientific understanding.

It is therefore apparent that a mechanism needs to be developed which will address, across all fields of animal biotechnology, the raising of public understanding whilst satisfying public concern that a common ethical standard and foresight is being applied in all these fields. There can be no doubt of the enormous potential benefits of animal biotechnology for the future of animal and human health and welfare. It is thus essential that issues of public acceptance are addressed effectively to ensure that the advancement and application of this technology is not hampered by unnecessary public concerns whilst due attention is paid to genuine concerns.

Evidence from SERC

SUMMARY OF POINTS

- SERC funds £10 million per annum of research and £2 million per annum of training in biotechnology.
- Collaboration with industry is a major feature of support.
- UK is well placed to claim a significant proportion of the expanding world market of biotechnology.
- Opportunities are in: drug development based on "small" proteins or chemicals; use of biocatalysts for synthesis; exploitation of genetically modified plants and materials; selective design of herbicides and pesticides.

- Main safety issue is genetic modification.
- Current UK regulations based on current EC legislatives and directives.
- SERC research mainly falls into Contained Use regulations, but increasing amount of work is being supported on environmental bioremediation.
- Regulations could impede, through delays and increased costs, bioprocess engineering groups working on scale up of laboratory experiments.
- Regulatory regime will not unduly prejudice the exploitation of the science base by UK industry.
- Public awareness is being addressed actively through BJAB.
- Need to maintain and develop science base in biotechnology and support advanced research and training in relevant technologies.
- Collaboration between science base and industry is essential.
- Biotechnology needs to be recognised as a long time investment, requiring a co-ordinated approach.

1. *What is your interest in biotechnology?*

The SERC supports research and training in biotechnology in HEIs to underpin the needs of UK industry. Through the SERC Biotechnology Directorate, some £10 million per annum is provided for the support of research and some £2 million per annum for research training (some 400 studentships current at any one time). Policy development in this area is assisted by a Committee comprising equal numbers of academics and industrialists. Collaboration with industry is emphasised both in the provision of research grant support (using the LINK scheme and collaborative grants) and training (via CASE awards). More fundamental research which may be relevant to biotechnology is also supported through the SERC Biological Sciences, Chemistry and Process Engineering Committees.

In view of the SERC's role set out above, it is best placed to answer questions 2, 3, 9i, 10, 11 and 12. Opinions are offered on some of the other questions however. The following paragraphs are numbered to correspond with the original questions.

2. *How and why is biotechnology important to UK industry?*

Biotechnology underpins some of the most successful industries in the UK, particularly pharmaceuticals and fine chemicals. UK pharmaceutical companies currently have some 15 per cent of the world market. Recent authoritative reports suggest a threefold increase in the sales of biotechnology-based products by the end of the century. The UK also has a strong research base in the biosciences. The UK is thus very well placed to claim a significant proprtion of this expanding market.

3. *What future prospects and opportunities does the technology offer?*

Currently 16 proteins manufactured by recombinant DNA (rDNA) technology are on the market as pharmaceutical products. This is expected to grow substantially. Future work in this area, exploiting rDNA techniques and receptor technology, is likely to lead to drug development based on "small" proteins or chemicals. The use of biocatalysts also offers the ability to manufacture chemicals with increased stereospecificity and, by replacement of traditional chemical routes, may offer more environmentally friendly modes of synthesis. Whilst not of such direct relevance to SERC, rDNA technology also offers substantial gains to the agricultural industry through both exploitation of genetically modified plants and animals and the design of more selective herbicides and insecticides.

4. *Which developments in biotechnology raise issues of safety?*

The principal concern, from a safety, and public acceptance, point of view, is that of genetic modification. Not all biotechnology involves genetic modification but it is in this area that many of the potential advances are to be made, particularly in healthcare and in agriculture.

5. *Should biotechnology be regulated by an industry specific regime?*

No. Biotechnology is not an industry specific capability.

6. *How do current regulations compare with those of other competitor countries?*

As with other EC Member States, current UK regulations are strongly based on current EC legislation and directives. However, local pressure groups in some countries (notably Germany, Denmark and Holland) have resulted in a more stringent and detrimental interpretation of the EC directives in those countries. In general through OECD there has been the deliberate policy of harmonising regulations as far as possible between Europe, USA and Japan. In the USA however, there is a move to make regulation less onerous.

7. *What are the consequences of the regulatory regime on the competitiveness of UK industry?*

There are now in place specific regulations which cover genetically modified organisms (GMOs), in addition to those which relate to chemical and process industries generally. The recently introduced GMO regulations were heavily criticised in their draft form, but the revised, published versions are much improved. As the Sub-Committee will be aware, the new regulations fall into two groups—Deliberate Release, and Contained Use. The research supported by SERC falls primarily, but not exclusively, into the latter category, and therefore subject only to one set of regulations. SERC is however supporting an increasing amount of work on environmental bioremediation, which could involve deliberate release of GMOs.

Within the Contained Use regulations, consents and fees should not be too much of a burden for many academic researchers, however there are some bioprocess engineering groups working on scale up of laboratory experiments who may be more severely affected, and whose projects could incur delays and increased costs. It is likely that this will place the UK at a slight disadvantage compared with the USA who have proposed (Quayle Report) to fast track both research and product development in the USA. Although the interpretation of the EC directives in the UK is not as stringent as Germany, Denmark and Holland it is more stringent than in the Mediterranean Countries (Spain, Portugal, Italy, Greece, etc) who are likely to thereby benefit by investment.

8. *Will the present regulatory regime prevent the exploitation of the science base?*

SERC does not believe that the present regulatory regime will prevent the exploitation of the science base by UK industry. Whilst there may be slight delays in comparison with the USA or Mediterranean Countries it is unlikely that the effect will be unduly detrimental. It may be offset by increased public confidence in the regulation of the technology.

9. *How can issues of public acceptance be addressed?*

Public awareness is a key issue, and is being addressed by the Biotechnology Joint Advisory Board (BJAB), which advises and co-ordinates the activities of all the Research Councils and DTI. In October 1992, BJAB held a major workshop on public perception which recommended that consideration should be given to the appointment of a subgroup with special responsibility for three main areas:

(i) Communications between the biotechnology community and other groups including the general public;

(ii) Education, particularly at the schools level;

(iii) Research to develop greater understanding of the mechanisms of public perception in biotechnology.

10. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry*

Realising the potential opportunities will depend on a number of other factors, not least the continued availability of new knowledge and techniques from the science base, and the availability of skilled manpower. It will be essential to maintain and continue to develop the science base in biotechnology and to promote and support advanced research and training in the relevant technologies. This will require significant investment in facilities particularly in the area of biochemical process engineering.

Collaboration between the science base and industry is also essential if ideas developed by the academic base are to have the opportunity of being exploited by UK industry. The LINK scheme has an important role to play here, and is already well utilised in this area.

It will be important for Industry and Government to regard biotechnology as a long term development and to invest accordingly. The timescales for development and exploitation are long; pharmaceutical products from biotechnology are likely to have a 10 to 15 year programme from inception to marketable product.

Biotechnology has applications in may diverse fields. The role of BJAB is crucial as a focus for DTI, the Research Councils, Industry and Academia to coordinate their activities and move forward together over a broad front.

Letter to the Clerk from R K M Hay, Scottish Agricultural Science Agency

Thank you for your letter of 19 February inviting me to provide evidence to Sub-Committee II—Regulation of the UK biotechnology industry and global competitiveness.

Dealing with your questions in turn:

1. The interests of SASA, as a Government Agency, lie in the areas of:

(i) The use and development of techniques to indentify indigenous and non-indigenous plant pests and pathogens.

(ii) The use and development of techniques to identify and discriminate between new and existing cultivars of crop plants.

(iii) The use and development of techniques to maintain and multiply pathogen-free nuclear stocks of crop plants, expecially potatoes for the whole of the UK. Associated maintenance and quarantine functions for imported cultivars.

(iv) The provision of advice to SO and SOAFD policy divisions on technical matters relating to the use of GM (genetically modified) plants and GMOs (genetically modified organisms) in Scotland, including representation or ACRE as The Scottish Office assessor.

(v) Licensing experiments on GM plant pests and pathogens in Scotland under the Plant Health (GB) Order.

2. Biotechnological techniques can make an important contribution to the maintenance and improvement of agricultural productivity, by protecting crops from non-indigenous pests and pathogens; by improving resistance to indigenous pests and pathogens; by allowing a reduction of pesticide imput; and by maintaining cultivar purity.

3. There are prospects to improve diagnostic techniques by making them more economical, rapid, effective, accurate or reliable and to produce new cultivars with increased productivity, resistance to pests and pathogens, or with special features which will enhance their utilisation, thus contributing to a more effective and competitive agricultural industry.

4. Molecular biology, as one component of biotechnology, raises important environmental safety issues but there would appear to be few, if any, human health and safety considerations arising from biotechnology in our areas of responsibility or interest. The reliance on biotechnology methods for maintaining and preserving genetic resources puts a high priority on their reliability, but this relates to the security of the conservation of diversity on a global scale rather than being a local or national safety issue.

5. The answer to this question depends upon how broad or narrow a definition of industry is used. Regulatory regimes should be derived from a logical consideration of techniques used, taking account of commonalities rather than the nature of the end product.

6, 7. Horizontal regulation (as defined in the question) is to be preferred logically, since if products with the same characteristics are derived in different ways they could be regulated and assessed by different standards, and even be subject to duplicate assessment by different authorities at different stages of development/use. For example, at present, genetically-modified pest/pathogens would receive scrutiny under GM regulations, which are enforced by HSE, and plant health legislation, which is controlled by SOAFD/MAFF.

8, 9. The Sub-committee is referred to an interim report of the EC Biotechnology Co-ordination Committee "Regulatory Framework and Research Policy Effort on Biotechnology in the EC and US", dated Brussels, 16 November 1992. This makes clear the dominant influence of the USA. There are also recent widespread developments in the Republic of China, but we have no detailed knowledge.

10. Probably yes, but minimal in the area of crop production unless constraints prevent comparative and registration trials being conducted in a normal and practical manner.

11. Public acceptance depends on confidence in the way earlier problems related to potential hazards, eg AIDS, BSE, etc have been addressed. Communication, and education from an early age, is essential, There is a need for an informed public so that communications can be understood. People are frightened of the unknown. Too small a proportion of the general public is aware of how things work—science is often looked down upon.

12. We are not in a position to respond to this question.

R K M Hay

Evidence from the Scottish Biotechnology Taskforce

SUMMARY

Biotechnology is important to both the development of new industry and the sustained competitiveness of existing UK industy. Biotechnology offers the UK the potential to exploit our strengths in fundamental life science research to bring economic and social benefits to the population. The appropriate regulatory environment is important to the competitiveness of industry and the acceptance of biotechnology by the general public. Products developed or produced using biotechnology do not, per se, pose any greater risks to the public than similar products produced by other means. The products of traditional biotechnology (beverages, dairy products, etc), have a long record of safety. A vertical regulation is proposed as the simplest, most cost effective and efficient form. Not only regulation per se, but the regulatory environment must be considered. The issues in biotechnology are wider than simple regulation but involve domestic capitalisation of investment in basic research. The development, protection and commercialisation of intellectual property is of key importance.

The Scottish Biotechnology Taskforce (SBT) is a co-ordinating body comprising the economic development organisations of: Scottish Enterprise, Scottish Office and representatives of industry and academia. The role of the SBT is to develop commercial biotechnology in Scotland.

Biotechnology is a key enabling technology that will have impact on the development of industries key to the UK economy eg Pharmaceuticals, Chemicals, Food and Agriculture. As an innovative technology, biotechnology stimulates the formation of new small and medium sized enterprises that are an important contributor to the creation of wealth and employment. Biotechnology will also enable existing industries to maintain competitiveness through the introduction of more efficient processes and new products.

According to a recent report by the Senior Advisory Group on Biotechnology which represents major European companies, 21.6 million people throughout the EC are employed in jobs that are, or will be, affected by biotechnology. Furthermore, Europe has the potential to create or secure over two million new jobs by the year 2000 through the introduction of biotechnology.

As commercialisation proceeds, new products derived from biotechnology offer unique solutions to the treatment of diseases such as cancer, cardiovascular disease, auto immune diseases such as arthritis and a host of genetically-linked conditions. Even where a drug is not produced biologically the techniques of biotechnology will greatly enhance the effectiveness of the drug discovery process.

In environmental technologies, biotechnology in the form of microbial bioremediation (without the need necessarily for genetically modified organisms), offers a solution to many intractable problems in land pollution and waste treatment. New diagnostic techniques will also be important in rapid and simple detection of potential environmental pollutants and pathogens.

Much of the fundamental research in the United Kingdom and particularly in Scotland is biotechnology intensive and directed at life sciences in general and in the medical/pharmaceutical area in particular. This investment in research provides an opportunity to transfer new technologies into existing business areas so that companies can maintain their international competitiveness. Application of new technology by small companies will contribute to rapid growth of highly innovative companies which can provide high quality employment with considerable spin-off economic benefit to their local community. It has been estimated that world sales of products derived from biotechnology will rise from a current £3.6bn to £60bn by the year 2000.

Many of the techniques and procedures employed on biotechnology do not differ significantly from those in more traditional areas of life science. Regulation of products developed or manufactured using biotechnology should reflect the potential risks. Most questions of safety relate to the use of genetically modified organisms (GMO) and these fall into two broad categories.

(a) *Contained use* where a process employs a GMO at some stage but does not appear as part of any released product. In these cases the safety of the product and the workplace should be regulated in relation to the risk presented using criteria similar to those applied to conventional processes. The risk to the public at large and the employees involved should be small provided suitable procedures are adopted.

(b) *Deliberate release* where the product consists at least in part of a GMO. In these cases sufficient product testing procedures must be required to ensure safety. It should be noted that many of the organisms being considered may arise naturally by normal mutation or be produced by conventional breeding. These processes are not currently regulated.

Biotechnology should not be regulated by a separate industry regime. This would create a mistaken impression that biotechnology products are inherently more dangerous than products derived from other processes. Such an approach may also give rise to an additional bureaucratic burden on industry and cause delay in introducing commercially important and beneficial products while it is decided under which authority they are to be approved.

The most effective and simple regulatory regime would approve products on the basis of product characteristics rather than process of manufacture. This approach adds no additional administrative burdens or additional costs to industry while providing protection for the public. Authorities currently charged with approving products have the most appropriate knowledge and experience to judge the implications and safety of new products. As an example, a therapeutic (whether genetically engineered or not), is most appropriately evaluated by the Medicines Control Agency. It is this approach which has been adopted in the USA and which, at least in part, has allowed the industry to flourish in that country.

The competitiveness of a nation is affected not only by regulations themselves but by its regulatory environment. Speed and sensitivity in the application of the rules and response to submissions made to authorities is a key factor.

An inappropriate regulatory environment will have a severe effect on the competitiveness of the industry in a number of ways:

1. Industry support for fundamental research in the UK would be reduced with multinational companies, for example, preferring to use other locations for discovery research.
2. Investment in product development would be curtailed in the UK, damaging biotechnology companies' ability to compete globally. Conventional industries employing biotechnology for example in processing or waste treatment would lose a competitive edge or be forced to relocate away from the UK.

3. Investment in new companies developing and using biotechnology would be reduced, damaging the prospects of creating the innovative companies which will provide economic growth through exploiting the emerging technologies.
4. Decisions in siting commercial biotechnology activity will be adversely affected by a severe regulatory regime. This affects not only existing companies and new company formation but inward investment projects particularly from the USA. For example, the regulatory environment in Germany has resulted in a number of large companies deciding to relocate their biotechnology efforts to the USA and France.

Regulators must find a balance between stringency of regulation and effective implementation which protects the public and at the same time allows industry to compete internationally.

Regulation of biotechnology in the hands of agencies which already have the confidence of the general public will assist in allaying fears which are the basis of public suspicion towards biotechnology.

In the UK we have an excellent science base but a notoriously poor record in the development of technology. The future of biotechnology in the UK depends on improving mechanisms of technology transfer from academia to industry. One of the limitations of technology transfer is the relatively small population of domestic companies able to commercialise technologies developed in our academic establishments. Thus not only technology transfer mechanisms but technology based company formation and development issues need to be addressed.

A significant factor in the commercial development of biotechnology in the UK is the ability of inventors to obtain strong patent protection. Such patent protection is vital to the commercial development of technology since investment in companies depends upon it. This is especially important to SMEs since intellectual property is often the major asset of the business. Patent problems ar exacerbated by the lengthy development times for biotechnology products, arising as a consequence of regulation, which reduces the effective period of patent protection. An adjustment of patent regulation bringing the UK into line with competitor nations (especially the USA), would benefit the development of industry in this country.

Biotechnology should be an important source of wealth to the UK. This may be limited not only by questions of appropriate regulation but also by fundamental problems in the exploitation of the UK's considerable investment in basic research. The approach to biotechnology should not be limited to questions of regulation but should encompass wider issues surrounding the commercial exploitation of biotechnology to create material and social benefits.

Evidence from the Senior Advisory Group (SAGB) Biotechnology

1. *What is your interest in Biotechnology?*

The Senior Advisory Group on Biotechnology (SAGB) comprises 30 companies, each with significant investment in biotechnology activities in Europe. The members of SAGB are engaged in all the industry sectors where biotechnology is increasingly being applied eg. healthcare, chemicals, plants and seeds, agriculture and food.

Annex 1 gives the membership of SAGB and their cumulative turnover and employment.

2. *How and why is Biotechnology important to UK Industry?*

Biotechnology is vital to the economies of all European countries. If industry in the UK and throughout Europe is not able to assimilate new technology on an equal footing to its major trading partners, then traditional industrial strengths will decline. Europe has much to gain from competitive use of biotechnology (and therefore much to lose if we do not get it right):

— industrial sectors (agriculture, chemicals, healthcare, food) in which the commercial impacts of biotechnology will be most significant, today account for over 21 per cent of European Community industrial production.

— the Community as a whole has more than 21.5 million jobs at stake in these sectors.

— these sectors account for approximately 30 per cent of Community exports.

In order for the UK and the rest of Europe to remain competitive and maintain these strengths in a world market, it is essential that companies are able to make full use of innovative technology.

It is interesting to note that the UK has traditional strengths in these areas.

3. *What future prospects and opportunities does the technology offer?*

Biotechnology offers a range of prospects and opportunities. For example:

— *products that cannot be manufactured otherwise,* particularly in the pharmaceutical field.

— *product improvements* and advances of benefit to consumers in areas such as human and animal health, diagnostics, plant breeding and food.

- *environmental benefits* through the increasing use of biotechnology. Industrial processes based on modern biotechnology often consume less raw material, water and energy than those based on traditional methods.
- *contribution to prosperity* through growth, employment and secondary economic activity around each stage of the investment cycle.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

The technology itself is neutral with respect to safety. It is neither indicative of safety or of risk. What is important in judging safety is the nature of the organism ie its characteristics and its intended use. In other words "what is the product in question" and not "how was it made". That is not to say that the use of live organisms is without risk but we draw attention to the fact that in Europe there is a tendency to regard the techniques of modern biotechnology (rDNA/genetic engineering/genetic modification) as inherently dangerous and worthy of special regulatory regimes. This runs contrary to much of the scientific advice available during the last ten years.

For example, an OECD Ad-Hoc Group of National Experts on Safety and Regulations in Biotechnology was set up in 1983. The Group's main task was to identify scientific criteria for the safe use of rDNA organisms in industry, agriculture and the environment.

Underlying the specific recommendations in the subsequent report (OECD, 1986) were the following fundamental points:

- Any **risks** raised by rDNA organisms are expected to be of the **same nature** as those associated with conventional organisms. Such risks may, furthermore, be assessed in generally the same way as non rDNA organisms.
- Although rDNA techniques may result in organisms with a combination of traits not observed in nature, rDNA techniques will often have inherently **greater predictability** compared to conventional methods of modifying organisms.
- There is no **scientific basis to justify *specific*** legislation for rDNA organisms—although the report recommended an examination of existing oversight mechanisms to ensure that adequate control may be achieved.

5. *Should biotechnology be regulated by an industry specific regime?*

The first point to make here is that there is no such thing as a biotechnology industry. Biotechnology is a set of tools applicable to many existing industrial sectors. Regulation must be oriented towards the class of product emanating from those sectors. To do otherwise creates confusion, overlapping regulations and excessive bureaucracy.

To go back to the question, industry should be regulated by a product specific regime related to an industrial class and not by a technique specific approach.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

From the above comments it is clear that SAGB believes vertical regulation to be better than horizontal. The reasons are:

- SAGB agrees with the majority of scientific opinion ie questions of safety stem from an organism's characteristics and use, not from the process by which it may have been derived.
- if products developed using certain techniques or processes are subject to specific regulations, then we are in danger of fragmenting the regulatory picture with overlapping and dual requirements.
- the end result is discrimination against the technique and consequent disincentive towards investment in modern biotechnology in Europe.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

Certainly regulation should evolve to a vertical approach. However the word "evolve" does not imply the sense of urgency that SAGB believes is necessary to restore confidence that Europe has got its act together.

Because of the tendency in Europe to focus on certain biotechnological techniques as a regulatory trigger, a major opportunity to put in place a coherent framework for the regulation of biotechnology has been missed. Rather than establish or review existing general legislation to ensure that the new techniques of biotechnology can be dealt with, a major legislative burden for industry and academia on certain types of technique has been instituted by EC directives that focus on GMO's (genetically modified organisms).

In the European Community we are as a result in danger of developing different regulations for rDNA biopesticides than for other biopesticides, different requirements for foods, containing rDNA microorganisms than for foods with microorganisms modified in other less precise ways, and different rules for rDNA live vaccines than for other live vaccines.

In commercial terms, it leads to dual approval systems or discrimination against the newer products of biotechnology and fragmentation of the regulatory picture. In turn this involves increased cost and regulatory uncertainty, both of which threaten investment, benefits and jobs. This also has upstream and negative consequences for research and development in academia.

8. *How do current regulations compare with those of other competitor countries*

The comparison between Europe, Far East and the USA can perhaps best be expressed in the attached diagrams.

It is clear that the European regulation describes better a "maze" than a coherent approach.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards:*

1. *research*
2. *product development*
3. *investment*
4. *location*
5. *sales and marketing?*

It is not appropriate for SAGB to answer this for the UK.

For Europe as a whole however, a recent poll of SAGB companies investment intention indicates that European-based companies applying biotechnology consider the United States to be a more attractive location for future investment than Europe. Also the Asian share of future European companies investment is predicted to increase significantly.

Considerable unease over the EC Directives on the "contained use" and "deliberate release" of genetically modified organisms was expressed by industrialists attending a seminar organised by the SAGB in September 1992.

Principle concerns centred on the complexity and over-centralised Commission control imposed by the Directives. Delegates also questioned the underlying basis of both Directives because they are technology-specific without adequately defining either the technology to be regulated or the objectives to be attained.

One of the major catalysts for promoting biotechnology's competitive economic benefits is the structure of the regulatory system. Correctly structured, the system will both encourage and ensure safety—wrongly conceived it will stifle growth without adding to safety.

Delegates concluded that the Directives were seriously restricting levels of investment within the EC in this vital strategic technology for Europe, leaving the field clear for the United States and Japan. They called for a more rational regulatory structure comparable to those operating in the rest of the world.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

This question cannot be specifically answered by SAGB for the UK but is also addressed above in the response to question 9.

11. *How best can issues of public acceptance be addressed?*

Much has been said and written on the importance of public acceptance of biotechnology.

Of course public opinion is important and it does have a bearing on issues such as regulation, intellectual property and, particularly on the way in which they are addressed through public policy by governments. But, the role of public policy is to balance the broad spectrum of interests of society and what sometimes seems to be forgotten in this process with respect to biotechnology in particular, is the variety of societal interests that are already affected and will increasingly be in the future.

For example to take the case of regulations, as noted above there is a tendency especially in Europe to focus strongly on the need to regulate against *postulated* environmental risks arising from modern biotechnology as almost the only public policy response to the technology. But this is against a background of no adverse effects to mankind or plants and animals and demonstrated safety and environmental improvements through the use of biotechnology. The point is that a public policy approach for biotechnology in the safety and environmental field must address *both* aspects of the topic ie the clear benefits in terms of environment and safety as well as the need for sound, science based regulations. Otherwise in the case of regulations, we risk getting into a self-perpetuating cycle.

supposed adverse
public opinion

impression of high risk ← bureaucratic regulations focused on the technology

The public is not being protected against real risk but being fed a dangerously negative image of the technology. Of course we do need regulations, particularly to ensure consistent product safety but they need to address scientific risk and take their place among a series of public policy measures designed overall to facilitate the use of the technology.

One thing seems clear—given the variation of public awareness and acceptance of biotechnology that exists depending on nationality, sector of application, historical and cultural differences etc., there can be no single answer to the question of public acceptance. We need a multi-factorial approach to communication that takes these variations into account and one that focuses less on the technology itself and more on what it can contribute to worldwide problem solving.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

This is not for SAGB to answer with respect to the UK. However for Europe as a whole, SAGB companies identify the following other factors as crucial for competitiveness:

- harmonised and effective intellectual property protection.
- the need to maintain European strengths in the basic life sciences through policy support for R&D investment.

ANNEX 1

List of SAGB Members

Agricultural Genetics Company Ltd.
Akzo Pharma
Amylum N.V.
Bayer AG
Boehringer Mannheim GmbH
British Biotechnology Ltd.
BSN Groupe
Celltech Ltd.
Ciba Geigy
Dupont
Eli Lilly International Corporation
Eurocetus B.V.
Ferruzzi Group
Gist Brocades N.V.
Hoechst AG
Hoffmann-La Roche Inc.
ICI
Innogenetics
Monsanto Europe S.A.
Nestlé
Novo Nordisk A/S
Orsan
Pharmacia Biotech AB
Plant Genetic Systems N.V.
Rhône-Poulenc
Sandoz Ltd.
Schering AG
Smith Kline Beecham
Solvay S.A.
Unilever Plc.

The combined total turnover of SAGB companies is $305 billion, they spend annually $17 billion on R&D and invest $24 billion in new plant and other facilities.

The SAGB companies provide employment for nearly two million people worldwide.

Evidence from Shell Research Ltd

SHELL has interests in the following areas of biotechnology:

(a) Evironmental applications; bioremediation and treatment of waste streams using traditional fermentation processes.

(b) Production of biopolymers by traditional fermentation techniques.

(c) Protein engineering; identification of new products and the development of novel methods to screen for bio-active compounds.

(d) Forestry biotechnology; genetic modification of Eucalyptus species used in commercial plantation forestry.

The application of biotechnology in these areas gives the possibility of identifying and producing novel products of processes and reducing production costs of existing processes. The overall prospects for the application of biotechnology in UK industry are good and there is the potential for the technology to be applied to a diverse range of industrial operations. Some applications of biotechnology do raise issues of safety. This is particularly so in the case of the genetic manipulation of micro-organisms capable of causing harm to humans or the environment. If such organisms are capable of reproducing and persisting in the wider environment and are inadvertently released, it may prove difficult or impossible to eradicate them. A comprehensive regulatory regime to prevent such an occurrence is therefore essential.

We believe that industry should not be regulated by an industry specific regulatory regime. The motives for using the technology have no bearing on safety and the regulatory regime should be robust enough to cater for all circumstances in which the technology is employed. From a technical point of view, the safety of products should be assessed under a vertical regulatory regime. The safety of any product (whether produced by biotechnological or traditional processes) is a function of the constituents and properties of that product. The safety of the product and the safety of the production process can be assessed independently and there are no technical reasons why there should be the linkage that occurs under horizontal regulatory regimes. It would be preferable if horizontal regulatory regimes evolved into vertical regimes as soon as is practical.

The regulatory regimes of all EEC member states are based on the same EEC directives and in theory should be similar. In practice, the interpretation of the various directives does differ between member states. Germany has virtually wiped out its industrial and public sector research involving genetic manipulation due to the rigorous interpretation and implementation of the directives. The situation is much more relaxed in some of the other member states. The UK is somewhere in between the two extremes in terms of interpretation of the directives.

SHELL has little experience of the Japanese biotechnology regulatory regime.

The USA seems to have an effective regulatory infrastructure which is implemented with the minimum of effort and bureaucracy. The system is simple, transparent, is run at no cost to the user. The staff of the regulatory agencies are often specialists in their fields and are able to give detailed advice concerning the regulatory process. Once sufficient experience has been gained in specific areas, the USA has been quick to implement notification-based regulatory procedures.

The main criticism that could be levelled at the present UK regulatory regime concerns the organisation and implementation of the legislation, rather than the content or interpretation. Some aspects of the regulatory regime which have been put in place as a result of the recent legislation are more bureaucratic than those which have been replaced, without significantly improving safety. In addition, the agencies do not have enough qualified staff, and in some cases the culture, needed to guide the practitioner through the system and give advice on implementation of the legislation. The result is that the system can sometimes appear bewildering to the user. The present regime therefore places an unnecessarily large burden on the industry and this situation does not nurture a climate which is conducive to investment in the biotechnology industry within the UK.

Evidence from Professsor A R Slabas, University of Durham

EXECUTIVE SUMMARY

Biotechnology is important to the UK for the following reasons:

1. It will allow for an increasing pull for agricultural products, particularly regarding crops for industrial use.
2. It will form the basis of providing new materials which can be used in the polymer and chemical industries.
3. It allows existing stock-piles of plant material which are in excess in Europe to be diverted to a real outlet in the chemical industry.

There are enormous economic and industrial gains which can be made from this technology. However, to be able to fully realise the potential of the area, appropriate legislation must be in place. This legislation has, on the one hand, to bear in mind appropriate safety factors, and on the other, to be in such a form which will allow realistically for the development of the research base which is required for commercial exploitation.

The market which one is concerned with is a multi-billion pound market per annum, an exclusion from this area of technology would make the UK no longer industrially competitive.

1. *What is your interest in biotechnology?*

My interest in biotechnology is in the development of new crops and micro-organisms for industrial use. This has been pursued both in *Industry*—Unilever, where I was Section Manager of Cell Sciences, directing its Molecular Biology Programme, and Academia—when I moved to take up the Chair of Plant Sciences at Durham. I have since established the main plant lipid research group in the UK, with strong support from research councils and industry (Zeneca (ICI) Seeds, Unilever, Nickerson Biocem, Croda Chemicals, King Seeds).

2. *How and why is biotechnology important to UK industry?*

Biotechnology is important to UK industry because it gives the opportunity of producing existing products by a new route or producing *novel* products. It also allows for a wider utilization of our Agricultural resource. *Examples:* (1) The biodegradiable polymer Polyhydroxybutyrate, cannot be produced in large quantities by fermentation without vast expenditure on extra capital equipment—the ability to produce it *in plants* overcomes this obstacle and allows for greater Agricultural use away from traditional food products; (2) New feed stocks of the chemical (polymer) industry, dicarboxylic acids, can be generated by *upgrading* existing vegetable oil, *by microbial fermentation,* these oils are currently produced in excess to demand and *stored* at vast expense. This has two effects: (a) the production cost of the valuable dicarboxylic acid is lower, and (b) it creates a demand for the Agricultural products, (3) new oils can be generated for the chemical industry *directly in plants* by gene transfer, for example an oil containing erucic acid at all three positions of the triglyceride backbone would have high commercial value. At present, ornamental plants *Nasturtium* and *Limnanthes*, are the only natural source. The ability to produce such an oil in rape seed will greatly increase the value of the crop. This would overcome the economic requirements of an EC subsidy for growing this crop and allow land previously marked for set aside to be used for industry use.

It is basically important to increase our production and manufacturing base and keep us competitive. New materials will be made cheaper as *bulk* feed stocks for the chemical industry. This will become more important for socio-economic reasons. If UK does not invest then we will be held ransom to other countries for the basal cost of our raw materials. It is also important as it opens up an enormous science base.

3. *What future prospects and opportunities does the technology offer?*

Partly answered in 2.

(i) Greater use of Agricultural land for production of *industrial feed stocks*—so overcoming limitations by set-aside.

(ii) *Adaptation of plants to greater extremes of environment* which in the very long term could be of great importance.

(iii) *Biological control of pests* by including pest control agents into plant genome so avoiding use of chemical control agents.

(iv) Availability of *new chemical compounds in mass quantities,* using a green route, which will open up new opportunities for products. At present a number of such compounds do not have a market as large enough quantities do not exist for testing and market penetration. A whole new economic route will develop for chemical raw material production.

(v) A reduction in the use of chemical methods of production is predicted which will be more environmentally friendly and reduce risk to those involved in manufacture.

(vi) Vegetable oils which are more amenable to fractionation procedures will be developed allowing for easier down-stream processing.

(vi) Therapeutical products such as antibodies, pharmaceuticals, produced directly in plants.

(viii) Animals developed specifically for allowing rapid testing of cures to human illness.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

Main Issues

(i) The release of plants which have been transformed with foreign DNA into the environment is a potential problem. *This is being* addressed, especially concerning potential movement of genetic information from species to species and design/containment of experimental material.

(ii) Use of plant material in food chains. There is a major lobby against recombinant tomatoes in the US. This however, is not really a safety issue but one of customer acceptance. With crops for *industrial* use this is not an issue.

(iii) There is concern about introducing genes into the human germ line cells. However, medical opinion at present is logically against the introduction of foreign DNA into humans *which can be inherited.*

5. *Should biotechnology be regulated by an industry specific regime?*

No. It is critically important that the academic quarter is considered separately, ie *research* and *commercial production* have different requirements for regulation.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

Vertical regulation is much preferred regulation. This is the accepted route for food products in the US.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

Not necessarily.

8. *How do current regulations compare with those of other competitor countries—in Europe—in the Far East—the USA?*

Europe—favourably at present. There has been a good attitude to allowing research in field trials, after due safety evaluation. I would not wish us to go to unrealistic German legislation.

Far East—Not known to me.

USA—We are less favoured. I do not believe that, nationally, we have accepted the concept of transgenic material as a route to producing what can be derived natural. For example, growth hormone in animals. There is general feeling in UK/Europe that content of growth hormone in animals should be kept to a minimum so they have outlawed animals produced with increased growth hormone in them. Unfortunately, there are major differences in US/Europe meat production processess, in US only males are used which have a naturally low level of growth hormone, even with growth hormone added to speed growth it is considerably lower than the natural level in females. Yet in Europe both males and females are used in beef production. Because of this difference in European Production methods we are exposed to a higher level of growth hormone—if we changed to the US production method even *with* males given growth hormone our level of exposure would be lower.

9. *What are the consequences or likely consequences of the regulatory regime on competitiveness of the UK industry, in particular as regards . . .*

(i) Research

UK research is very competitive internationally, in lipid research we are at the cutting edge. If regulation becomes tighter we would cease to be given the opportunity to be competitive. Researchers would leave for countries where they could conduct the research, so restricting development, and also losing the best academics in the country.

(ii) **Product development**

Product development is tied into biotechnology. It: (a) needs the research base to design/invent new materials; (b) has to have the *availability* of new experimental materials to *test* for products. Unless biotechnology is firmly established in the UK then the development will be starved and we will become non-competitive. It is a concept of how long it takes to get a product developed from a lab bench or field into the market-place:

(iii) **Investment**

This would decrease in biotechnology, pharmaceuticals/Agriculture if it is seen we cannot be competitive. I am particularly concerned that with crops for *industrial use* we have enormous potential which still has to be realised. This will give in greater sustained demand for Agriculture with all the economic benefits.

(iv) **Location**

If major UK industry cannot do its research/production in UK, then it will be moved elsewhere for economic reasons.

(v) **Sales and Marketing**

Sales will inevitably go down unless we are competitive. There are many green issues here for chemical production/sustainable agriculture. Unless UK actively encourages development of new crops and production routes they will be produced in other countries giving them a *lower basal cost* in manufacture which will hit out sales at the most sensitive point, i.e. (1) availability of raw materials; (2) range of products which can be produced without patent infringement.

Marketing angles could also be lost, for example, oils produced using less environmentally damaging processes, biofuels—this has consumer awareness issues which affect sales.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

Some danger is present. We need to expand what will become acceptable *viewed* as a *product* and not so much as in *process*. I am particularly concerned that EC directives could try and alter UK legislation which is currently under review.

11. *How best can issues of public acceptance be addressed?*

There has to be an open long-term exposure of the public to these issues, expressing the concerns scientists have and what precautions are being taken by them. This might have to start at the school level. Certainly articles in the national press on "Frankenstein's Tomatoes" do not help. We should perhaps demonstrate benefits which the public can easily relate to, such as by human gene therapy. The food issue will always be sensitive. I would push crops for *industrial use* as there is no food connection and it is less sensitive.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

(i) Establishment of key research groups with long-term funding in central areas. This includes bringing the right people together in one place. To a large extent it is driven by personal drive.

(ii) Provision of key research staff to enter industry.

(iii) The extent to which the Government *directly back developments* in this area. It should also be realised that large companies, for patent reasons, will always wish to work with other research workers but not other industries. The LINK initiatives should not be set about pulling industry together as this is an erroneous concept.

(iv) Close consideration should be given to patenting issues in this, ie patenting genes which are isolated.

(v) Fostering collaboration with other countries key to the development of this area internationally.

(vi) Key biotechnologists need to interact with Government departments.

Evidence from SmithKline Beecham Pharmaceuticals (Dr Janet Dewdney, Director and Vice President Biotechnology Europe)

1. *What is your interest in biotechnology?*

SmithKline Beecham is a major pharmaceutical company dedicated to R&D, manufacturing and marketing products to serve international health care needs. Biotechnology represents a critical core technology to the Company which is being exploited to further its discovery and development of new medicines by

- the discovery and development of new biopharmaceuticals and vaccines.
- the use of cloned human receptors and other human proteins to expedite the discovery and development of new chemical entities in key areas of clinical medicine.
- the discovery of novel microbial metabolites from fermentation.
- improvements in fermentation processes leading to yield improvements and economic advantages, in relation to existing product ranges.

In addition, SmithKline Beecham has a substantial interest in diagnostics and in the impact of biotechnology on its diagnostic business.

These activities relate to the Pharmaceuticals business of the Company. SmithKline Beecham also has a major commitment to Consumer Products and will, as the opportunity arises, use the tools of biotechnology to develop new products or improve the processes by which existing products are manufactured.

SmithKline Beecham is therefore at the forefront of the exploitation of the key technologies understood to fall within the term Biotechnology and is deeply concerned to ensure that the regulation of these technologies creates opportunities for global competitiveness in research, development and manufacturing and Company success.

2. *How and why is biotechnology important to UK industry?*

The Pharmaceutical Industry is a highly successful industry with an outstanding record of scientific innovation which has contributed directly to the nation's health and bolstered the UK economy over a number of years. The Industry's competitive position, however, cannot be guaranteed. It must continue to embrace new technologies and grasp the opportunities they offer if it is to remain in the first league on a world basis. Biotechnology is one such technology and comprises tools, reagents and processes which are essential if the Pharmaceutical Industry is to retain its innovatory leadership position.

Biotechnology is also a key route to innovation in other industrial sectors. These include the food processing industry, agriculture and the chemical industry.

3. *What future prospects and opportunities does the technology offer?*

Biotechnology is viewed within the Pharmaceutical Industry as a major source of innovatory opportunity. This is not pure speculation and hyperbole. Already the seeds of the biotechnology revolution are bearing fruit as exemplified below.

Biopharmaceuticals are protein agents derived by biotechnology and which offer opportunities to treat a range of serious and life threatening conditions currently inaccessible by more conventional drug approaches. It has been said that the application of biotechnology to produce novel biopharmaceuticals will generate a new Pharmacopoeia. That new Pharmacopoeia is already emerging.

The definition of biopharmaceuticals used here includes monoclonal antibody therapeutic opportunities, a dramatic advance based on original research carried out in the UK.

By 1995, the pharmaceutical industry as a whole is expected to have a turnover of around $180 billion of which 5 to 10 per cent could be biopharmaceuticals; taking the USA alone, biopharmaceuticals may represent, by the year 2,000, 15 to 20 per cent of US industry sales. CEST. *Biotechnology as a Competitive Advantage*. 1992

This growth in biopharmaceuticals has already started. 1990–91 sales of biopharmaceuticals were reported to be over $4 billion.

Process Improvements

Processes within the fermentation industry, which include those fermentation processes used by the Pharmaceuticals Industry for the manufacture of therapeutic medicines, are equally impacted by biotechnology. Even highly advanced and optimised processes such as those within SB for the production of penicillins can be significantly improved by biotechnology processes, including gene duplication for yield improvement. Thus genetically-modified organisms are already contributing to our manufacturing processes and this application will continue into the future.

In addition, many manufacturing processes use enzymes for biotransformation; SB probably dominates this field with its use of amidase enzymes in the production of ß-lactam penicillins, The use of biotransformation in the production of chemicals and medicines is expected to grow in response to advances in biotechnology which will contribute, inter alia.

- a means of providing large quantities of rare enzymes.
- catalytic antibodies to mimic enzyme activities.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

It is important to remember that biotechnology is not new. Fermentation technology, which involves modification of organisms for improved biomass, growth characteristics or secondary metabolite production, is one of the most long-standing and established technologies with benefits in pharmaceuticals, foods, brewing and so on.

The safety record with respect to both **process** and **product** has been exemplary.

The question perhaps should be redefined to ask do the recent advances in biotechnology i.e. the ability to manipulate DNA and transfer genetic materials from one organism to another and hybridoma technology (the ability to make antibodies in cell culture) which created the era of new biotechnology and all its promise, being with it special safety considerations or risks?

It is important to repeat that genetic manipulation is not new nor is it inherently unsafe. Nonetheless, no scientific or government body would argue that because of our current safety record, no control or regulation is required. Indeed in the UK we have addressed this control through:

The Health and Safety at Work Act

The Control of Substances Hazardous to Health Act

and The Genetic Manipulation Regulation.

What then are the new safety issues raised by advances in biotechnology?

Within pharmaceuticals, whether R&D or manufacturing, there are no additional risk factors. Use of genetically-modified organisms (GMO's) can be regulated on the basis of risk factors which have been applied safely for over a decade. Key to the risk-categorisation is that GMO's are disabled with respect to survival in the environment and of predictable properties as they contain known gene sequences. GMO's are thus arguably safer than organisms manipulated at random. In addition, all operational facilities provide for accidental release by use of special containment/destruction technology. These points are especially important in scale-up operations and are exemplified by risk reduction procedures taken within our own organisation.

Answers to this question underline very forcibly that genetic manipulation is not inherently unsafe. Risk factors are different for each industrial sector and must be considered on that basis. For pharmaceuticals, the product be safe and effective and the process must confirm to regulation. For transgenic plants it is self-evident that different issues arise, for example, transmission, ecological effects. Thus, we emphasize again that sector regulation is more relevant, appropriate and effective than any attempt to impose horizontal regulation into product registration activities. This is further discussed under Question 5.

5. *Should biotechnology be regulated by an industry specific regime?*

SmithKline Beecham is in accord with that of the Pharmaceutical Industry as a whole in believing that regulation shoud be industry specific.

The regulation of new medicines, including all licensing activities, is well established and is effective in ensuring that new medicines introduced to the market are of high and consistent quality, are effective and are safe under the prescribed conditions of use.

While it is clear that we, the pharmaceutical industry, share a common commitment with other industries to the set of technologies and tools encampassed by "biotechnology" and to economic forces, our product-related concerns are different and unique to our product range.

This is an important concept. It is potentially damaging to the UK's competitive and economic advancement to promulgate the view that there is a "biotechnology industry". This merely obfuscates important issues of safety, risk assessment and public acceptance and creates the opportunity to make "generic" statements which may have applicability only to limited industrial activities.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

It is self-evident from the reply to Q5 that we hold strongly to the view that vertical product regulation is both acceptable, and logical and has stood the test of time. Horizontal regulation superimposed upon product, vertical regulation creates, within the European regulatory arena and thus, within also the UK, a bureaucratic and demanding set of procedures which will impact adversely on European competitiveness and not add to product safety.

It is self evident that process regulation is required for research and development activities; there is no product at that stage. This type of regulation as noted earlier has been in place for many years and could have been adequately modified to encompass genetic engineering without recourse to a new set of GMO-specific regulations.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

It is not a question of evolution. Vertical regulation is appropriate with respect to products, however made. Horizontal regulation concerns process.

I believe the control/regulation in place already in the UK has laid the foundations for effective further regulation if needed.

8. *How do current regulations compare with those of other competitor countries*

- *in Europe*
- *in the Far East*
- *in the USA?*

The attached illustrations state more clearly than words the difference in regulation in competitor countries. (Ref. SAGB. 1992.)

The EEC passed two Directives covering biotechnology; the contained use of GMO's 90/219 and the deliberate release of GMO's 90/220.

Member states were required to implement by October 1991, a date which was not met in the UK and most other countries due to the need for extensive clarification and change.

It was the extremely poor quality of these Directives and the intention to apply them horizontally across all sectors that resulted in unnecessary confusion, negative attitudes and bewildering complexity—a triad of problems united in the word bureaucracy.

The US and Japanese systems of regulation are no less stringent and this is an important point. What they are is transparent, a natural extension of existing legislation, a recognition that the sector interests are different, and above all comprehensible.

From a Pharmaceutical Industry viewpoint, the modification to the Directives prior to implementation into UK legislation has removed much that was of deep concern to us. There are still a number of detailed matters which need clarification and/or change, and we will continue to press for action on these points.

In addition, we are well aware of other draft Directives currently under consideration by the EC. Many of these are specifically addressed to GMO's. This is of major concern to all sectors and is creating a continuing environment of uncertainty in Europe.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards*

(1) *research*

(2) *product development*

(3) *investment*

(4) *location*

(5) *sales and marketing?*

SB is a transnational pharmaceutical company with R&D operations in the UK, USA and Continental Europe. Any regulation or economic regime which makes the UK less competitive than these other countries will encourage us to invest outside the UK.

Research & Development

The changes to the regulation under The Genetically Modified Organisms (Contained Use) Regulation 1992 as regards R&D activities are as follows:

1. The regulations repeal and replace all previous GMO legislation.
2. The regulations cover both human health *and* environmental risks.
3. Organisms are now classified as Group I (non-hazardous) or Group II (any organism which may be considered hazardous).
4. Work is now classified as Type A operation (work for R&D purposes capable of containment by standard laboratory means) or a Type B operation (production scale).
5. (i) Group I Type A work will require annual notification to HSE.
    (ii) Group II Type A work and Group I Type B work require a notification to HSE 60 days in advance of the work commencing and is subject to a fee of £180 per notification.
    (iii) Group II Type B work requires formal consent applicaions which may be consulted by the public. Applicants may request information to be withheld on the basis of commercial confidentiality.
6. An Emergency Plan must be prepared for any Group II Type B work. This plan must review emergency procedures in the event of an accident and be developed in association with the emergency services, National Rivers Authority etc.

7. All work must be assessed and approved by a properly constituted Genetic Modification Safety Committee. Assessments must review risks to health and safety, and also risks of environmental damage.

The main additional assessments required under the new law relate to environmental damage. Of major concern is the uncertainty over pilot plant scale working within R&D. If the Type B designation is applied to R&D activities on a scale larger than 10 litres then this will severely hinder our R&D activities and cause delay and expense.

Manufacturing

It is anticipated that most fermentation-based activities on a production scale in the Pharmaceutical Industry will be within the classification Group I, Type B. The 60 day prior notification requirement will create the possibility of significant delays and impact adversely on time to market entry. Were Group II, Type B operations to be undertaken, the the further restraints and public access to the documentation would create additional concerns and delays. Any significant delays in the production process which impact on the market entry time of new products create unfavourable competitive positions for industry.

Investment/Location/Marketing

SAGB is currently working on an analysis of the biotechnology investment cycle. It states, in summary, that uncertainty over regulation and lack of public education and support is inhibiting investment in biotechnology in Europe.

The public perception aspect of this argument is important. If the public is led to believe that GMO's and genetic engineering is intrinsically unsafe they will fail to give support in many of the biotechnology applications discussed earlier. The EC emphasis on GMO specific regulation is creating this environment.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

There is evidence that this is already happening. Major European companies are choosing not to invest in manufacturing plant (involving GMO's) in Europe and the UK is undoubtedly losing out in equal measure.

SB is currently exploring options for a manufacturing plant for biopharmaceuticals. In spite of a strong research base in the UK, it is unlikely that Europe will be chosen for the plant; regulatory attitudes and a general unease over biotechnology, are not necessarily the critical decisive factors, but do play a part in the decision process.

From a research perspective, we need experience of working under the new regulations before we can comment fully on how restrictive they will be. Issues such as the definition of scale-of-working are still under debate. For example, if the Directives limit of 10 litre scale for Group A operations were to be implemented, then a major constraint would be put upon our research competitiveness.

11. *How best can issues of public acceptance be addressed?*

The public acceptance question is one which illustrates well the importance of sectional focus on biotechnology issues.

In health care, there are relatively few public acceptance issues at the current time although we have highlighted below issues which might become more publicly visible in the next decade. Ill people require therapy and can rightly expect the health care industry to provide therapeutic medicines and prophylactic measures to control disease (vaccines). The process by which such medicines are discovered, developed and manufactured are not, in general, an issue.

Contrast this situation with other industies for which biotechnology is a key to problem solving and standard of living benefits such as novel foods.

There is an emotional and poorly understood or expressed antipathy in small but vocal groups within the community to "genetically-derived" foods, as indeed to irradiated foods which preceded them. The arguments in favour of these developments are economically driven and not seen by the public as impacting favourably on them as individuals, or on their communities.

Any attempt to "change" public opinion and attitudes and to educate, will only be effective if adequately targeted. If attempts are made to educate to "generic" biotechnology it will surely fail.

For the pharmaceutical industry therefore our task is to ensure that the public knows about and appreciates the value of biotechnology applied to health care. The industry has reality not dreams to relate to the public. Within SB, we point to the use of genetically-engineered vaccines, notably Engerix B to control/prevent hepatitis B infection and to the use of genetically-modified micro-organisms to improve production processes for semi-synthetic penicillins. Numerous further exemplifications, further back in the development pipe-line can be quoted.

We return now to the issue raised earlier in this Section. Will public concerns impact upon our industry in the future? Two topics should be addressed.

i. The Use of Transgenic Animals

Transgenic animals are used within the industry for two main purposes.

- As models of human disease in drug discovery initiatives.

  The public needs reassurance on the welfare aspects of this advance pointing out the benefits in terms of standardization and reliability resulting in the need for fewer animals and on the elimination of human disease creation in animals to mimic the clinical situation. Both of these are strong points but "the public" is not yet fully conversant with the arguments.

- As providers of human proteins for therapeutic use.

  The technology allows for the use of targeted ways of effecting secretion of human proteins in milk and there are other applications also. Again the public needs to be educated and reassured as this technology develops.

ii. Gene Therapy

There will be significant impact of gene therapy on the Pharmaceutical Industry, an impact not yet forwarded nor fully appreciated. Again, the public will be behind the Industry in exploiting gene therapy in disease. It will on the other hand require a major public acceptance campaign to reassure the public on issues such as eugenics, modifications within the germ line etc.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

- Erosion of the UK science base and failure to address industry needs for appropriation scientists (for example, fermentation scientists, protein engineers).
- Uncertainty over patients and intellectual property rights.
- Investment confidence which in turn feeds back on R&D expenditure and commitment.
- Economic climate which discourages, or fails to encourage venture-capital investment in biotechnology.
- Over emphasis on health care cost containment at a time of unprecedented medical opportunities.

Evidence from the Society for General Microbiology

1. *Interest in Biotechnology*

The Society for General Microbiology has many members who are involved in the teaching of courses relevant to Biotechnology and also many who are involved in research projects which are directly concerned with biotechnology and its enabling disciplines. Others are employed in Research Institutes and Industrial laboratories working directly in the development of biotechnological products. As a society with direct interests in biotechnology, which also supports the science through its activities, we wish to make the following points in relation to the effects of regulation on the global competitiveness of UK Biotechnology.

2. *Importance of Biotechnology to UK Industry*

The UK has strength in several of the industries (pharmaceutical, health care and agricultural, etc) which are concerned with biotechnology. There is no real biotechnology industry as such. The role of biotechnology in producing new products in a number of these areas is paramount. UK has considerable expertise in many of the disciplines required to initiate new developments and products.

3. *Future Prospects and Opportunities offered by Biotechnology*

In many areas such as vaccine development, improved diagnostic procedures, gene therapy, new antimicrobial agents, etc "biotechnology" offers the prospect of rapid and novel advances in a manner which traditional approaches do not. Some of these offer excellent potential for commercial success if they receive adequate scientific input and financial support.

4. *Which developments raise issues of safety*

There is an innate fear by the general public of "genetically engineered microorganisms, animals and plants" and they require assurance that all developments incorporate safety checks and that the final products are themselves inherently safe.

8. *How do current regulations compare with those of competitor countries*

The UK regulations are probably comparable with those in the Netherlands and in Denmark—countries which have similar biotechnological interests but which have specialist interests such as industrial enzymes in which they have a world market role. The regulations here are certainly less restrictive than those in Germany and Switzerland where current legal restrictions have greatly hindered biotechnological developments and have caused certain firms to move their operations elsewhere.

In the Far East, certain regulations are less restrictive (eg, those involving food in Japan) while others appear to be similar to those in the UK and the US. Some Far East countries appear to lack well defined regulatory procedures.

9. *What are the consequences of the regulatory regime on competitiveness?*

Research is likely to be significantly inhibited by certain proposed schemes for regulation. Any requirement for expensive annual schemes for recertification at the University or research institute level at which many projects are initiated will be an effective disincentive to many researchers in the enabling disciplines. Effective regulation must not stifle the relevant research with excessive costs and bureaucracy.

Product development is less may well be inhibited by highly restrictive regulations.

10. *Prevention of exploitation*

The present UK regulatory scheme appears to work reasonably well. There is certainly a need for an effective dialogue involving all parties potentially involved—universities, research institutes, industry and government—at all stages when regulation is changed or developed.

11. *Public acceptance*

The UK has not so far had to suffer from the extreme antagonism and vandalism seen in Germany or the Netherlands or from people such as Jerry Rifkind in the US, but acceptance cannot be taken for granted and there is a ground swell of antibiotechnology feeling which could well be mobilised. The COPUS scheme of the Royal Society and similar mechanisms using knowledgeable and excellent communicators are essential and should if possible be extended. The Parliamentary Office of Science and Technology should be strengthened and Government made more aware of the problems and potential of the Biotechnology Industry.

12. *Other Factors*

The UK must have a core of highly trained and adequately financed researchers capable of initiating the enabling research. The current lack of financial support at the University level and lack of a career structure which will attract and retain the best of our young scientists in the enabling disciplines bodes ill for the future of UK Biotechnology and plays into the hands of our competitor nations. Small companies with good product potential also require a supportive financial regime which will enable them to take their products to the market; Local Enterprise Companies have probably a key role to assist in marketing, development advice, etc.

The UK must ensure that EC support of Biotechnology is well planned and directed and the cooperation seen in some of the projects to date has been beneficial to our science base. It has however also given potential competitors a well-educated group of young scientists against whom we must now compete effectively.

Evidence from the Swiss Federal Office for Education and Science, Berne

1. *How important does your government perceive biotechnology to be?*

The Swiss government has repeatedly said that it considers biotechnology to be a promising new technology with great potential in health care, agronomy, food production, environmental improvements and nanotechnology; it also clearly expects Swiss industries to promote biotechnology. This support, expressed in several official documents, is perhaps best exemplified by the launching in 1992 of a federal programme of research in biotechnology, for which over 50 million Swiss Francs have been committed until 1995.

2. *Which developments in biotechnology are thought to raise safety issues?*

Primarily, environmental impact of deliberate or accidental release of genetically modified organisms (microorganisms, plants and animals); also, efficiency of containment measures in closed systems (primarily microorganismus) in connection with safe working conditions, finally, public health concerns related to the use of biotechnology for food production.

3. *In your country, is biotechnology regulated by a specific regulatory regime?*

In May 1992, a new article of the Federal constitution was adopted by a majority of the people and of the cantons. It creates an obligation for the federal government to enact appropriate legislation regarding genetic engineering and reproduction medicine. The corresponding laws and implementing regulations are currently in preparation. The Swiss government has decided not to prepare a comprehensive "gene law" but rather to modify, wherever possible, existing laws and rules.

4. *Do regulations distinguish between contained use and general release?*

The planned legislation will indeed make that distinction.

5. *Is regulation in your country "horizontal" or "vertical"?*

Basically, the planned legislation will apply the same regulatory criteria to all products regardless of the process by which they have been obtained; thus, vertical regulation is clearly preferred. The main exception will be the compulsory notification and (in some cases) authorisation procedure required for certain projects involving recombinant DNA technology, in compliance with CEC Directives 219 and 220.

6. *Is biotechnology publicly accepted in your country?*

Current public acceptance is not very high, especially in the German-speaking part of Switzerland. Several groups are actively questioning biotechnology as a whole or specific aspects, such as safety issues or the question of patent protection for organisms.

Evidence from Professor Joyce Tait on behalf of ESRC

Points 1–11 below provide answers to the questions posed in your paper inviting evidence to your committee. Under point 12, I have reproduced a section from a report to the DTI to indicate how the marketing environment, risk regulation and public attitudes interact with one another to determine the future competitiveness of the UK biotechnology industry. Some points are covered in more detail in publications or conference papers, as indicated in the reference list. Copies of these papers can be supplied to the Select Commitee if required.

1. *What is my interest in biotechnology?*

My interest in biotechnology arose out of my earlier involvement in the 1970s and 80s with research on the agrochemical industry and pesticide usage by farmers. During the past five years I have been lead researcher on three major research projects studying agriculture-related developments in the biotechnology industry:

strategic and R&D decision making in large and small biotechnology firms, funded by ESRC/SERC Joint Committee, with Dr J Chataway;

risk regulation in agricultural biotechnology, funded by ESRC, with Mr L Levidow; and

public attitudes to biotechnology, funded by DTI, with Dr S. Martin.

The evidence in this response thus relates specifically to agricultural biotechnology. The team involved in this research has a large body of empirical data that enables us to understand the interactions between industry, government and the public in the development of a new technology.

I have attempted to answer most of your questions, but I am better qualified to comment on questions 5–11 than the others.

2. *How and why is biotechnology important to UK industry?*

A strong presence in biotechnology is esssential to the future competitiveness of the UK agrochemical and food industries. Without it they will be unable to retain an involvement with high value-added products.

Agricultural biotechnology could also enable UK farming practices to become less environmentally damaging while retaining current levels of productivity although, as we note below, marketing rather than regulatory factors are the main constraint preventing this from happening.

Because of its excellent pool of scientific expertise in relevant areas, the UK should be very well placed to build up an industry of world importance in agricultural biotechnology, provided some of the constraints referred to below can be dealt with.

3. *What future prospects and opportunities does the technology offer?*

This question will be beter answered by managers working in the industry.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

We have been particularly concerned with the issues raised by the release of genetically manipulated organisms (GMOs).

We have noted in our research on biotechnology regulation that laboratory-based scientists tend to be much more sanguine about the risks involved in the release of GMOs than are ecologists. This appears to be related to the reductionist approach of the laboratory-based scientists, compared to the more holistic approach of ecologists. Given the uncertainty and potential complexity surrounding the release of living GMOs to the environment, it would seem prudent to give at least equal weight to the views of ecologists. However, the norm is to give more weight to the views of laboratory-based scientists.

As regards the question of how the risks should be addressed, it is notable that the biotechnology industry is the first to be regulated, from the earliest stages of research and development, on a proactive, precautionary basis[1]. This approach was initially accepted by industry but, over the past few years they have become increasingly resistant to it and have been heavily engaged in lobbying against it, at national government and EC levels through organisations like the Senior Advisory Group on Biotechnology (SAGB) based in Brussels, Even among those who support a precautionary approach to regulation, there are many who do so from a desire to allay public fears, and not because they see a need to avert any real risks[2].

The precautionary approach is seen to be justified in circumstances where there is a high degree of uncertainty or complexity, along with a potential for seriously adverse environmental impacts, all of which apply to biotechnology. The UK system of regulation set up under the Environmental Protection Act 1990, and administered by ACGM and ACRE, is a well-informed and, on the whole, effective way of implementing this precautionary approach. Attempts to diminish its precautionary nature prematurely should be resisted, both on grounds of environmental risk and, as indicated in (12) below, because of the likely negative impact on public perceptions of the industry.

5. *Should biotechnology be regulated by an industry-specific regime?*

The key to the composition of the regulatory regime is largely in the nature of the expertise needed to predict the risks as accurately as possible. It is therefore unlikely that a single regime could cover the range of expertise needed to assess the risks of both agriculture—and drug-related developments. However, this problem would not be resolved by, say, giving assessment of the risks of pesticidal GMOs to the Advisory Committee on Pesticides (ACP). The risks posed by a GMO are likely to be very different from those posed by a pesticidal chemical, and addition of the necessary expertise to the ACP would be wasteful and administrative cumbersome. The example provided by ACRE in the UK would appear to be the most efficient solution, with the relatively scarce expertise needed to assess the risks of releasing a particular GMO concentrated in a single committee, which initially scrutinises all GMO products before they are passed on to the appropriate committee(s) to be scrutinised as a food, pesticide, or indeed both. This point is closely related to that raised in (6) below and the argument will be extended there.

6. *From a technical point of view, is horizontal regulation better than vertical regulation.*

A discussion of this issue is the main point addressed in the Futures article (see Reference 1). The article, based on an analysis of the claims and counter-claims made by industry and regulators, shows the horizontal regulation can be equated to a proactive, precautionary approach to risk regulation, while so-called vertical regulation is equivalent to a reactive, preventative approach. Industry's desire for vertical, product-based regulation is therefore a facet of its rejection of the precautionary approach to risk regulation which, I believe, has serious implications for the eventual acceptance of such approaches in orther areas of risk regulation such as pollution control.

A precautionary approach is applicable where either the level of uncertainty or the complexity of a situation means that it is difficult to predict the outcome of any course of action. Whether horizontal is better that vertical regulation, from a technical point of view, depends on whether one believes that the degree of complexity and/or uncertainty involved, and the seriousness of potential adverse outcomes are sufficient to justify its costs.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

If horizontal (precautionary) regulation is justified on grounds of uncertainty, then it should become less justified as we gain experience with the new technology, and it would be acceptable for it to progress towards a vertical approach.

We should, however, consider the possibility that, as uncertainty about individual products declines, complexity will increase. With increasing numbers of GMOs on the market, being used increasingly frequently by ordinary farmers, perhaps in unexpected combinations, the scope for interactions among GMOs and between GMOs and non-GMOs will increase enormously. This may provide justification for retaining a horizontal approach into the foreseeable future.

8. *How do current regulations compare with those of other competitor countries?*

Such comparisons are very much in vogue, often coupled with a threat from industry to move their operations to another country if the home government does not relax its regulatory regime to correspond with that of a competitor nation. Within the EC there is a serious attempt at harmonisation of biotechnology regulation, although there are still considerable differences between countries in the application of the regulation. France has had a large number of releases compared to other EC countries, but provides very little information about them. In the Far East, China appears to be imposing very few restrictions on the release of GMOs. Until the recent change of administration in the USA, its regulatory regime was much less restrictive than that of the EC, although this is now likely to change.

There are three major factors to be considered in this area:

> As in the USA, a change of government can lead to a change of regulatory regime. It would therefore be foolhardy for a company to move its facilities to another country purely for regulatory reasons. One would always expect there to be other, more pressing reasons where such a move is contemplated.
>
> A product has to satisfy the regulatory criteria of the country in which it is to be marketed. There would therefore be little point in testing a high value-added product destined for a market in Western developed countries in a country like China.
>
> Major multinational companies are increasingly sensitive about their public image. To be seen to be developing products in a more relaxed regulatory environment, in order to avoid meeting stringent home-country standards, could lead to a backlash in public opinion.

9. *What are the (likely) consequences of the regulatory regime on competitiveness of the UK industry?*

As explained in the response to Question 12, problems that are attributed by industry to the regulatory regime often have other contributory or major causes, for example the difficult marketing environment in the case of agricultural biotechnology. However, our research on R&D strategies showed that regulation, and associated issues related to public perception, did have a major impact on the decision making of small biotechnology companies, but little real impact on the large companies. Small companies found it difficult to cope with the long lead times to get a new product to the market and therefore tended to avoid working with GMOs where possible. The multinational companies operating in this area, on the other hand, are used to operating with such long lead times and have the resources and internal operating procedures in place to cope with them.

Regulation also affects investment in small companies, in that it delays the start of the payback period and venture capital will seek a more rapid return on its money elsewhere. This is not such a serious problem for multinational companies.

The importance to investors of potential markets for products, rather than regulatory regimes, is illustrated by the recent moves by the London Stock Exchange to make it easier for biotechnology companies to sell shares in the UK. Non-pharmaceutical companies are likely to be excluded from the scheme. This reflects the much more buoyant state of the drugs and health care markets, compared to agricultural markets, worldwide (see 12 below).

I do not believe that the regulatory regime itself has a major impact on location strategies, as indicated in (8) above. A wide range of factors affect location decisions by companies and, as noted above, it is the regulatory regime *in the country where products are to be marketed* that is more important to a company than the regime where the production facilities are located, at least for such high value added products.

Our research on public attitudes to biotechnology indicates that, by reassuring the public that products have been tested and are safe, a stringent regime actually assists marketing and sales (see 11 below).

As the above summary indicates, regulation has a major impact on small companies, and much less impact on large multinationals. The effects on the competitiveness of UK industry are therefore not straightforward. Because of the constraints under which they operate, small companies are forced into a state of dependence on multinationals (see endnote 3). For example, in our research project, one small company was inhibited from going into the plant breeding area because this would bring it into competition with one of its major large collaborators. The product strategies of the multinational companies strongly reflect their past history, often as agrochemical companies. In the IT industry, the multinational companies were in the same position, but innovative small companies were able to develop new ideas independently, often forcing large companies to change their strategies. In agricultural biotechnology, small companies are never likely to be in such a strong position and so the strategies of the multinational companies will remain dominant.

The overall impact or regulation, coupled with other constraints on development in agricultural biotechnology, is therefore not so much on the competitiveness of UK industry *per se*, but rather on the nature and pace of innovation, and hence the kinds of development that reach the market place.

10. *Is there a danger that the present regulatory regime will prevent the exploration by British industry of research conducted in the UK science base?*

For the reasons outlined above and in (12) below, I do not believe that there is a significant danger of this happening. The real constraints on the exploitation of research arise mainly in areas other than regulation. Indeed, we should be considering how regulation can be used constructively to create markets for new biotechnology products and to provide a stimulus to the industry, as was the case during the 1970s for the pesticide industry.

11. *How best can issues of public acceptance be addressed?*

Our recent research reports for the DTI describe the results of a major survey dealing with this issue[4 5]. In general we found that most members of the public, and indeed many members of environmental pressure groups, had not yet given thought to the issues surrounding biotechnology developments. For this reason we also paid particular attention to likely sources of influence on their future opinions.

In general we found that:

groups with an identifiable interest in biotechnology will probably already have, or will readily form, stable attitudes to it;

such groups will seek information and advice preferentially from sources likely to reinforce their existing attitudes;

once formed, such attitudes will be difficult to change;

some applications of biotechnology may be more controversial than is commonly supposed (for example making crops to grow in the Third World, or making medicines);

the groups with the least polarised current attitudes to biotechnology were most open to a wide range of sources of influence and advice.

From our evidence, the commonly held view that providing people with more information about biotechnology will make them more favourable disposed towards it, was *not* supported. The two groups most knowledgeable about the technology were the most favourably and the least favourably disposed towards it, to a highly significant extent.

Regarding the release of live GMOs to the environment, 91 per cent of respondents felt that the public should know about it, but only 25 per cent thought that they *would* be told about it. In this context it is interesting to note that two of our subsamples were of members of the public living near to release sites in Cornwall and near Oxford, and that very few were aware that releases had taken place in their neighbourhood. The system currently in place to inform the public about releases is therefore not working very well.

One other relevant finding relates to the perceived trustworthiness of sources of advice, information or opinion. In general, across all groups surveyed, the most preferred sources were: Friends of the Earth, Greenpeace, New Scientist magazine, conservation groups and scientists who work in universities, in that order. Working up from the bottom of the list were: tabloid newspapers, multinational companies, Department of Trade and Industry, small companies and the Government. Given that public attitudes are still largely unformed, it is worrying for the industry that its credibility and that of the Government is so low, and that groups likely to adopt anti-biotechnology attitudes have such a high level of credibility.

The key to public acceptance of the technology is to increase public trust in the industry, and unfortunately the activities of industry over the regulatory issue are likely to diminish, rather than increase public trust, as explained in (12) below.

12. *Other factors likely to play a crucial role.*

See integrative analysis reproduced in Appendix 1.

1.. Tait, J and Levidow, L (1992) Proactive and Reactive Approaches to Risk Regulation: the Case of Biotechnology. *Futures,* April 1992, 219–231.

2. Levidow, L and Tait, J (1992) Release of Genetically Modified Organisms: Precautionary Legisation. *Project Appraisal, 7(2), 93–105.*

3. Chataway, J and Tait, J (1933 in press). Is Risk Regulation a Strategic Influence on the Biotechnology Industry. *Agriculture and Human Values.*

4. S. Martin and J Tait (1992) (i) *Release of Genetically Modified Organisms: Public Attitudes and Understanding—Main Report* (pp 135); (iii) *Biotechnology: Cognitive Structures of Public Groups* (pp 56). Available from Centre for Technology Strategy, Open Univesity, Walton Hall, Milton Keynes MK7 6AA.

5. S Martin and J Tait (1992) Attitudes of Selected Public Groups in the UK to Biotechnology. In ed. J Durant, *Biotechnology in Public: a Review of Recent Research.* London Science Museum, pp 28–41.

APPENDIX I

SYSTEMIC ANALYSIS: THE EVOLUTION OF PUBLIC ATTITUDES TO BIOTECHNOLOGY AND THEIR IMPACT ON INDUSTRY STRATEGIES

This section develops a dynamic model of the interactions among various pressures influencing industrial investment in agriculture-related biotechnology. Based on this model and the results of the survey described here we offer suggestions for future scenarios for the evolution of public attitudes to biotechnology and their impact on the industry.

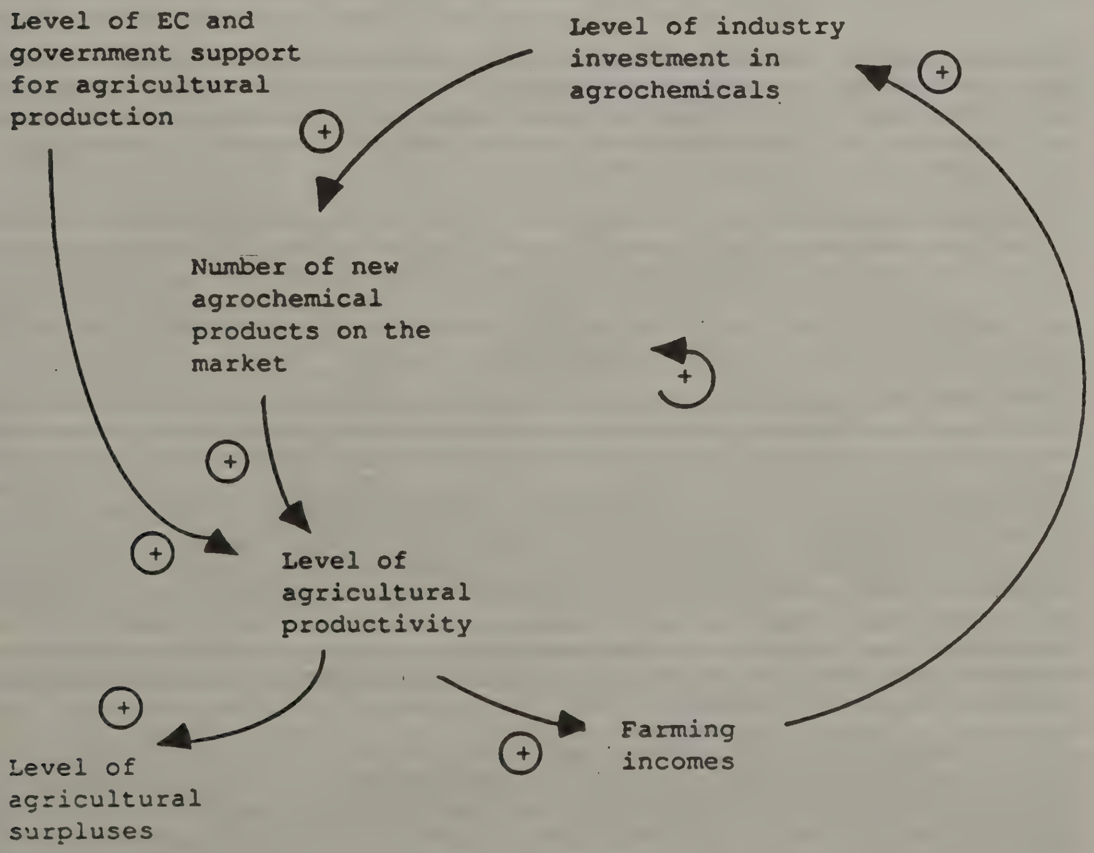
6.1 *Biotechnology Innovation: the Drivers of Industrial Investment.*

Many of the companies currently involved in biotechnology innovation were also very active in the agrochemical 'revolution' of the 1960s and 70s. The nature of the system supporting the heavy investment in R&D over this period, as described in Figure 6.1[1], is very relevant to industry's current expectations for new biotechnology developments.

Working round the positive feedback loop in Figure 6.1, a high level of industry investment in agrochemicals in the 1960s and 70s led to an increase in the number of new agrochemical products on the market, resulting in increased levels of agricultural productivity, followed by increases in farming incomes. As farming incomes increased, industry investment in R&D was further increased because of the perceived opportunities for yet more sales of agrochemicals. This positive feedback loop was thus behaving as a virtuous circle, from industry's point of view, continually encouraging increasing investment in agrochemicals R&D. The fuel which kept this feedback loop going was 'EC and government financial support for agricultural production'. The fact that a continually increasing level of agricultural surpluses was an outcome of this feedback loop was seen as a cause for some concern, but was not directly addressed.

Towards the end of the 1970s, this situation became unstable for two reasons. First, the level of agricultural surpluses became unsustainable and there was political pressure to cut back on support for agricultural production. Secondly, the agrochemical industry itself began to approach a state of 'maturity' where there were effective, cheap products available for most crop protection problems. Companies therefore began to look around for new outlets for their creativity that would enable them to remain 'high-tech', rather than become producers of commodity chemicals. Biotechnology was seen to provide this opportunity, leading to major investments, as described by a senior manager from Monsanto (Metz, 1984).

Figure 6.1 System Supporting Industrial Investment in Agrochemicals in the 1960s and 70s.


Level of EC and government support for agricultural production
Level of industry investment in agrochemicals
+
+
Number of new agrochemical products on the market
+
+
+
Level of agricultural productivity
+
Level of agricultural surpluses
+
Farming incomes

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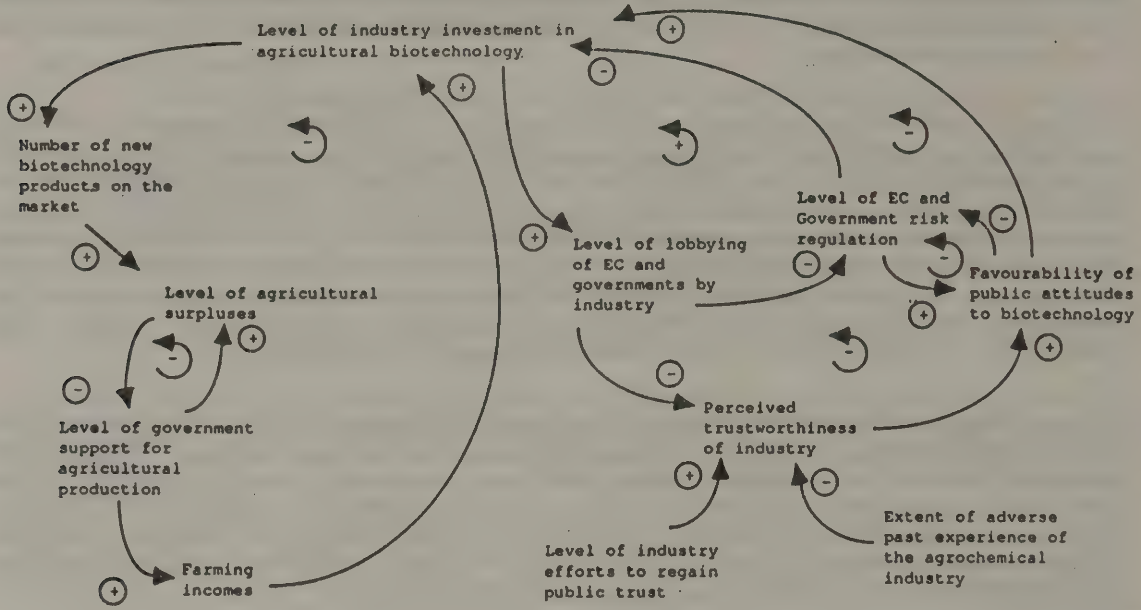
[1] In Figures 6.1 and 6.2, the following conventions are used: arrows show 'causes' or 'influences'; a negative sign on an arrow indicates a reciprocal relationship between two variables (as one increases, the other decreases), and a positive sign a direct relationship (both variables increase or decrease together); positive or negative feedback is indicated by the sign in the centre of the loop enclosed in a circular arrow.

Figure 6.2 System Supporting Industrial Investment in Biotechnology Products in the 1980s and 90s.


Level of industry investment in agricultural biotechnology
Number of new biotechnology products on the market
Level of agricultural surpluses
Level of government support for agricultural production
Farming incomes
Level of lobbying of EC and governments by industry
Level of EC and Government risk regulation
Favourability of public attitudes to biotechnology
Perceived trustworthiness of industry
Level of industry efforts to regain public trust
Extent of adverse past experience of the agrochemical industry

The feedback loop that had fuelled the prosperity of the agrochemical industry for the two previous decades had, however, changed. As shown on the left hand side of Figure 6.2, the level of agricultural surpluses and the level of government support for agricultural production have now become an integral part of the feedback loop. The resulting change to negative feedback means that this part of the system is now operating so as to inhibit industry investment (Tait *et al.*, 1990; 1991).

Other factors have also become increasing important. The central loop in Figure 6.2 describes the positive feedback system operating around the issue of risk regulation. The high level of EC and national government risk regulation is seen as an additional threat to industry's investment in biotechnology, leading to a high level of lobbying by industry. This is currently showing signs of being effective, reducing the level of risk regulation and hence encouraging investment. There is therefore, at least potentially, another positive feedback system, again operating as a virtuous circle a manner favourable to industry.

When the market situation for new pesticide developments was very favourable (Figure 6.1), this regulatory feedback loop was a less important factor in industry's decision making. In the current much more difficult marketing environment, it is assuming a major role. Other possible influences on the "risk regulation" variable are now therefore of serious concern to industry. If the favourability of public attitudes to biotechnology (shown on the right of Figure 6.2) were to become (or some would say remain) a stronger influence on EC and government than industry's lobbying, the virtuous circle would be converted to a vicious one, with a downward spiral of investment by industry. (An increase in the level of risk regulation would lead to a decline in industry investment; as investment declined, the incentive and the resources to support lobbying of government would decline; as the level of lobbying declined, the level of risk regulation would increase, particularly if there were public pressure in this direction, and so on.) Negative public attitudes to biotechnology also have a direct influence on industry investment, particularly for small companies, as indicated on the figure (Tait *et al*, 1991).

The dilemma faced by industry, as shown on the bottom right of Figure 6.2, is that the lobbying activity, through which they are attempting to maintain the regulatory feedback loop in "virtuous" mode, is also likely to diminish industry's perceived trustworthiness, and hence reinforce adverse public attitudes. The latter would then feed back, directly and through pressure to increase the level of risk regulation, to cut back on industry investment.

Two other important, and conflicting, variables affecting industry's perceived trustworthiness, are the extent of the public's adverse past experience of the agrochemical industry (mainly resulting from its association with pesticides) and the industry's current public relations efforts, at considerable expense, to regain public trust.

The models in Figures 6.1 and 6.2 thus illustrate the context within which the survey described here was carried out. The variable "favourability of public attitudes to biotechnology" now occupies a key position in the system influencing the level of industry investment in agricultural biotechnology. As this survey has shown, public attitudes are likely to be subject to a wide range of influences. Here we attempt to predict the direction and extent of some of these influences, and their resultant effect on the model as a whole.

6.2 *Future Development of Public Attitudes.*

Several of the issues raised by this survey seemed particularly relevant to future industry decision making on the promotion of, and investment in, the biotechnology industries. We have categorised these issues under four main headings: (i) a cluster of connected issues related to knowledge, information, attitudes and behaviour; (ii) the acceptability of different applications of biotechnology; (iii) the role of regulation both as a response to public attitudes and as a future influence on them, and the associated issue of public involvement in decision making; and (iv) the influence of various sources of information on future attitudes to biotechnology.

6.2.1 *Information, Knowledge, Attitudes and Behaviour*

In many cases our initial speculation, that the groups chosen would have had at least a minimal amount of information about biotechnology and would have begun to form attitudes towards it, proved over-optimistic. Among those chosen for interview, the employees of the multinational company had been directly targeted with information. Some of the members of the public living near GMO release sites had been informed as members of the local district council or had been involved in making objections to a release; many others in these samples appeared completely unaware of the fact that they were living near to the site of a release. Members of environmental public interest groups were also much less well informed than we had expected. Among the questionnaire respondents, the university researchers were, well informed, the next most knowledgable group being the Network for Alternative Technology and Technology Assessment. In the other cases, the general public and the public interest group samples, the overall level of knowledge was low.

It is commonly assumed that providing more and better information about biotechnology will lead to more public knowledge about it, that better knowledge will be reflected in more favourable public attitudes and that these attitudes will then lead to correspondingly favourable public behaviour, or at least to lack of opposition. However, the results of this survey appear to challenge several of the links in this chain of events.

There was virtually no awareness among the NCW and OXF groups that they were living close to sites where GMOs had already been released. The present arrangements, requiring local District Council approval of releases, following a press announcement, are intended to ensure an element of public consultation in the regulatory process. However, even in North Cornwall, where there had been objections to a proposed release and follow-up articles in the press that were much more eye-catching than the original advertisement, this had not resulted in widespread general awareness. Given that a number of respondents said they would be concerned if they thought releases were taking place near them, one cannot assume that the current arrangements for information provision will actually lead to local knowledge of releases or will avoid conflict in future when the number off releases reaches more commercial proportions.

The assumption that more knowledgable people will also be more approving of biotechnology was not borne out by the results of this survey. The two most knowledgable groups in terms of general education and of self assessment of their understanding of biotechnology (SCI and NAT) were located at opposite extremes of the spectrum of favourability towards biotechnology, with highly significant differences in their responses to most questions. It would therefore not be appropriate to attempt to seek correlations between level of knowledge of biotechnology and the favourability or otherwise of various components of attitude.

The lack of prior information and knowledge about biotechnology has been seen as a problem for attitude surveys on the assumption that, without this information, people could not form attitudes. However, where interviewees or questionnaire respondents have little previous knowledge, but are prepared to give serious consideration to an issue, they will attempt to integrate it into their pre-existing set of attitudes to other issues that they perceive as being relevant.

It was clear from our interviews with members of environmental interest groups that they had a ready-made framework within which to conceptualise biotechnology. Having already thought through their attitudes to related issues, when asked about biotechnology, they could fit it into this system so as to avoid the uncomfortable state of having mutually incompatible attitudes (cognitive dissonance). As members of a group of people with shared attitudes they will be exposed through meetings and newsletters to influences which will reinforce this attitude system, so their attitudes to biotechnology, once formed, will be reasonably stable. Among the environmental groups included in the questionnaire analysis, UGG was much less active, with few opportunities to reinforce shared attitudes, and it is notable that its members also had a greater range of scores on attitudes to biotechnology and social influences than the other two environmental groups.

The two public groups in North Cornwall and Oxford were not organised in any cohesive way relevant to the subject of the survey. A few individuals may have been members of environmental or other groups that would provide them with a framework into which to integrate stable attitudes to biotechnology. However, it is likely that the majority were expressing attitudes that would be relatively malleable and more open to change under future influences than any of the other groups. It is therefore notable that the OXF and NCW groups were open to a wider range of influences than the other groups, where the tendency was to seek or accept information from groups with opinions similar to their own.

It is generally accepted that there is a relationship, although frequently not a straightforward one, between attitudes and behaviour. With products not yet available on the market, the ordinary member of the public does not have many opportunities to engage in positive behaviour towards biotechnology. However, we did ask questionnaire respondents whether they would be prepared to eat various genetically manipulated products. There were strong demands for information, and for foods whose development or preparation has involved genetic manipulation to be labelled as such. There was also a considerable number who would not be prepared to eat genetically manipulated products, particularly meat or fish, although less so in the MNC and SCI groups.

At the present stage of development of the technology, there are more immediate possibilities for negative action in the form of objections to releases and we also tried to find out to what extent people would be happy with genetically manipulated crops being grown near where they live and would be prepared to do something about it if they were not. It was interesting to note the large proportion, particularly in the NCW group, but also in OXF, who would not be happy with this situation, and who would be prepared to do something about it if they thought it was happening.

As noted above, the relationship between attitudes and behaviour can be a complex one. For example, an individual may gradually build up an increasingly negative attitude to a particular issue over a period of time, without this being expressed in any overtly identifiable behaviour. In such a situation, a small incident can trigger a reaction that is apparently out of all proportion to the stimulus. Alternatively, the attitude-behaviour response may be sensitised by a previous and apparently unrelated event so that again a small stimulus results in an apparently excessive response. As an example of the latter, it was widely held among the regulators who became involved in the public objection to the proposed release in North Cornwall that this had little to do with biotechnology *per se*. They believed that public distrust of local regulatory authorities had been severely damaged by an earlier incident involving pollution of drinking water, resulting in automatic rejection of a wide range of potential developments. Although this is a plausible explanation, from the perspective of attitude-behaviour relations, there was no evidence from our interviews that it was true in this instance.

6.2.2 *Acceptability of Different Biotechnology Applications*

As has been the case with previous surveys of public attitudes to biotechnology, we found that medical applications were considerably more acceptable than agricultural ones. Among the agricultural applications, there was a wide variation in their overall level of acceptability, although in general genetic manipulation of plants was most acceptable and of animals and humans least acceptable. There appeared to be two dimensions to the concept of acceptability in the minds of respondents: in the case of animals and humans, ethical issues predominated; for micro-organisms, particularly viruses, there was greater concern about risk-related issues and our ability to control the organisms once released into the environment. In the latter context there was notably greater concern about *releasing* genetically manipulated plants and micro-organisms than there was about their being genetically manipulated in the first place. With animals, however, in keeping with the likelihood that this is purely an ethical issue, there was no increase in the level of concern about actual releases.

The overall levels of concern expressed, among all the groups, were high. This leads us to the tentative conclusion, a worrying one from industry's perspective, that these negative attitudes may be triggered into overt expression in behaviour by some relatively minor event, as described above, or as more trial releases take place and products appear on the market.

The results of this survey also suggest that it may be helpful to reconsider what should be regarded as "controversial" applications of biotechnology. For example, even issues like "medical research", "cleaning up oil slicks", "curing diseases", or "detoxifying industrial waste", normally seen as uncontroversial, elicited a wide range of opinions from the different groups (Table 4.5). In many cases, comments written on the questionnaire or made during interviews suggested that these differences were due to fundamental differences of worldview among respondents—a feeling, particularly among the environmental groups, that biotechnology was part of a "technical fix" approach to environmental management and as such should not be encouraged. Using biotechnology to "feed the Third World" also came into this category, as well as being regarded with considerable scepticism by many respondents. These findings again should cause some concern to the industry, indicating as they do that when public attitudes to biotechnology do become more clearly formulated, they may revolve around fundamentalist, value laden issues rather than being pragmatic and interest based (Tait, 1988).

Another factor which appeared to be very important in determining the acceptability of biotechnology products was its perceived worth or need. Given that most of the people involved in this survey had not been taking an interest in the issue of biotechnology regulation, it is unlikely that they would have been aware of the debate surrounding the concept of a "Fourth Hurdle". This spontaneous expression of concern by large numbers of respondents is in keeping with the general trend, also notable in this survey, for the public to want to be involved in technological decisions which affect their lives but which they feel powerless to influence. Industry's forceful rejection of the proposed Fourth Hurdle may therefore again prove counter-productive to its attempts to facilitate the development of biotechnology products.

6.2.3 *The Role of Regulation*

In Figure 6.2, the small feedback loop connecting "level of regulation" and "favourability of public attitudes" implies that a high level of regulation will reassure the public about the risks of agricultural biotechnology, as was assumed by those involved in drafting Part VI of the UK Environmental Protection Act, dealing with the release of GMOs (Levidow and Tait, 1992, in press). However, many scientists and industrialists believe that, on the contrary, a high level of regulation will merely generate unnecessary public alarm.

The results of this survey did not support the latter interpretation. Given the almost complete lack of awareness of the regulatory situation for biotechnology among the survey population, the relatively high levels of concern could not be attributed to this. On the contrary, there was a general feeling that regulation would not be sufficiently strict, that the technology was open to misuse, and that there should be careful monitoring of releases.

The industry strategy of lobbying for less stringent regulation of biotechnology is motivated, at least in part, by considerations that have nothing to do with public opinion, as described above. However, an important part of the calculation of the costs and benefits of this strategy should be its impact on public attitudes and hence its possible reflection, at a later date, in overt negative behaviour.

6.2.4. *Future Influences on Public Attitudes*

Where interviewees already had a coherent set of attitudes towards biotechnology or related issues, there was a predictable bias towards sources of information and advice that would tend to reinforce these attitudes. Those with less clearly developed attitude systems had a wider range of potential influences on their attitudes.

However, in keeping with the results of other recent attitude surveys, there was a strong basis, across all groups, away from industry and government as respected sources of information and towards environmentally-based organisations. The most popular sources of information and advice were those that were perceived to be negative, or at least neutral, towards biotechnology. Even among the MNC group, multinational companies ranked only ninth (equal with farmers and conservation groups) in likelihood of acceptance as a source of information.

As indicated above, the NCW and OXF groups could be seen as closer to representing uncommitted members of the general public than any of the others. Table 4.19 shows that they gave high ratings to environmental groups (with the exception of animal rights organisations) and relatively neutral sources like New Scientist, scientists in universities and the quality press. Low acceptance ratings were awarded to tabloid newspapers, multinational companies, the DTI, small companies and, particularly relevant in the regulatory context, District Councils.

Because of the likely importance of the various sources of influence in determining future public attitudes to biotechnology, questions 10-15 of the questionnaire explored respondents' attitudes to these sources in more detail (see Tables 4.21-4.35). In interpreting these tables, it is important to consider the actual percentage of favourable answers towards each of the bodies, in addition to the relative order of favourability in each case.

The MNC group was most favourably disposed towards companies, albeit with only 24 per cent favourable answers. OXF was the next most favourable group while NCW was one of the least favourable. For central government bodies, OXF, MNC and NCW were the three most favourably disposed, although again with a fairly low percentage of favourable answers (less than 26 per cent). A similar pattern emerged for district councils, but this time with less than 11 per cent favourable answers.

As regards favourability towards environmental groups, NCW and OXF were in the middle of the range, but this time with 42 per cent and 35 per cent favourable answers respecrtively. They were even more favourably disposed towards media and television with 64 per cent and 63 per cent favourable answers respectively. Scientists, on the other hand were given a much lower rating, with only 18 per cent and 19 per cent favourable answers.

There did not appear to be a direct correspondence between attitudes to the various information sources, and likely acceptance of their view, as indicated in Table 4.35.

Although these tables do indicate that the two public groups, OXF and NCW, were less prejudiced against industry and government than some of the other groups surveyed, the figures for the average percentage of favourable answers towards these groups are very low. On the other hand, although they appear less favourably disposed than most others towards environmental groups, the figures for the average percentage of favourable answers are much higher than for industry and government.

It is also relevant that the information sources with the highest proportion of favourable answers were the ones most likely to adopt a fundamentalist, value-based position on biotechnology, so that it may come to be regarded, like nuclear power, as a technology which is basically unnaceptable. If these sources should prove to be the most influential, industry's rational arguments about national or consumer interests would carry very little weight.

6.3 *Scenarios for Industry*

Section 6.1 set up a model of the complex interactions linking public attitudes to industry investment in biotechnology, and section 6.2 has summarised the major implications of our survey results that are relevant to this model.

Given the large amount of uncertainly surrounding the future development of public attitudes, it seems appropriate to consider two very different future scenarios (Schwartz, 1991), one positive and one negative from industry's point of view, and to consider the impact of industry's current strategies on these scenarios.

6.3.1 *Scenario 1—the Best Outcome*

Within the next five to ten years we can expect to see an increasing number of products on the market that involve the release of GMOs. Based on the model in Figure 6.2, the ideal outcome for industry would be a level of risk regulation that is at least no greater than that currently applied to foods and pesticides. The lobbying necessary to achieve this would not have had a negative impact on the perceived trustworthiness of industry and efforts to regain public trust would begin to pay off as adverse past experience of the agrochemical industry faded from public memory. As part of this scenario, one would need to assume that there had been no adverse environmental or other impacts arising from the release of GMOs, at the trials stage or as fully developed products.

Even this very favourable scenario for the feedback loops on the right hand side of Figure 6.2 would probably not be sufficient to fuel major levels of industrial investment if agricultural markets remain in their present depressed condition. However biotechnology itself, and particularly GMOs, may hold the key to removing this restriction if it can provide new uses for agricultural land that do not involve food production, for example the growing of crops as feedstock for the chemical industry or for use as renewable sources of fuel, or the growing of crops or animals to produce new generations of drugs. For this strategy to be successful, it would also require that these "high-tech" solutions do not trigger adverse public reactions of a fundamentalist nature.

6.3.2. *Scenario 2—the Worst Outcome*

The worst case scenario, as explored to some extent already in section 6.1, would be one where industry lobbying triggers a backlash that results in serious further loss of public trust, more than negating its current efforts to regain that trust. The resulting public pressure on governments would then lead to unnecessarily high levels of risk regulation, depressing industry investment.

With investment depressed, and high levels of regulation, there will be fewer biotechnology-based products available to provide alternatives to food production for agricultural land, so agricultural markets will remain depressed, further discouraging industrial investment. Under this scenario, it is also likely that the biotechnology products which could provide these alternative land uses will attract serious public opposition as yet another technical fix from an industry which is not to be trusted.

6.3.3 *Industry Strategies, Current and Future*

(i) Choice of Biotechnology Project

Several elements of current industry strategies for the promotion biotechnology appear likely to encourage the second, worst case scenario, given what we have learned about public attitudes from this survey.

Among the most high-profile of the early developments of biotechnology are bovine somatotropin (BST) and herbicide resistant crops. In the context of the issues raised by this survey, BST involves the manipulation (of not yet the *genetic* manipulation) of animals; it will increase the production of milk, for which there is no perceived need; it supports the further evolution of high input, technologically-based agricultural systems; and, at least in the UK, the trials stages of its development have been conducted in an atmosphere of great secrecy.

Herbicide resistant crops are generally seen as likely to lead to increases in herbicide usage, although industry claims that this will not be the case. It is harder to argue, however, that they do not support high-input, chemically-based crop production systems of the type opposed by many members of the environmental groups involved in this survey.

The development of insecticide-resistant crops, on the other hand, would not be subject to this criticism, but even where companies are working on them, they do not promote the idea particularly actively. Presumably, it is a difficult decision for an agrochemical company to promote a new technology which may undermine one of its major existing sources of revenue.

(ii) Industry's Promotion Strategies

We have already described industry's current lobbying strategy as regards risk regulation, and pointed out some of its dangers. However, industry's statements as regards risk regulation are, if anything, becoming more uncompromising as time goes on. This situation arises from a deliberate decision, taken a few years ago by a powerful group of multinational companies, to spend less effort on direct communication with the public, to attempt to reduce the public profile of the technology and to concentrate their efforts at the national government and EC level.

A quantitative analysis, comparing the potential cost of negative public attitudes against the cost of complying with more restrictive regulatory regimes, at least until the technology has proved itself in practice, may well indicate that the present strategy is not a cost-effective one. There must be many managers in the nuclear power industry who now regret the expensive years spent in uncompromising confrontation with the public.

Even at the more straightforward level of public relations and advertising, industry's current approach may not be as sophisticated as this survey would suggest it needs to be. The outcome of an expensive advertising campaign claiming that biotechnology will feed the Third World could merely be a greater scepticism about industry's real motives. In interviews with managers from multinational companies (conducted as part of another research project) several stated that they would not be developing products for Third World countries because these countries could not afford the high prices needed to cover the R&D costs. Statements made by interviewees and additional comments written on the questionnaires indicated that, even if it were believed, such a strategy could not count on even majority support among environmental groups who were more highly regarded as an information source than multinational companies.

(iii) Information Provision and Public Involvement

Industry is strongly resistant to demands for more public involvement in decision making about new technology or even for more information to be provided, two issues which were particularly important to many of the people we surveyed. Commercial confidentiality is frequently cited as the reason for secrecy and for restricting access to regulatory decision making. However, at least in the UK, managers from commercial companies *are* involved in regulation and decision making. If they have access to the data and information on other companies products it is difficult to argue, on grounds of commercial confidentiality, for the exclusion of the general public.

(iv) "New, Improved" Strategies

Based on the results of this survey, we believe that public attitudes to biotechnology may now be in a fairly finely-balanced state. They have not yet become negatively polarised, but a single high-profile incident could trigger such a process. Many of industry's current strategies, as described above, seem likely to generate such incidents. We therefore believe that a re-examination of these strategies, comparing the cost of abandoning them against the cost of alienating public opinion, is desirable from industry's point view.

Evidence from the UK Agricultural Supply Trade Association Ltd

1. *What is your interest in biotechnology*

The United Kingdom Agricultural Supply Trade Association (UKASTA) represents over 400 companies involved in the supply and marketing of crop production and animal feedstuff manufacturing. Member companies may be involved in the marketing of genetically improved seed stocks, the purchase and marketing of the subsequently produced crop and the inclusion of these crops into animal feed compounds. The feed manufacturing industry must also recognise the existence of genetically improved livestock whose nutrient requirements may be significantly different to existing strains.

2. *How and why is biotechnology important to industry?*

UK industry benefits from the wide base of common knowledge available from standard molecular biology. This provides a strong conceptual inter-strain within industry, linking biotechnology achievements between industry sectors.

There is a benefit to the public, both financial and environmental from increased efficiency in the production of human food products, both from arable crops and animals. Environmental benefit will be obtained from the reduced usage of chemical inputs which will, in turn, reduce both food costs and the UK reliance on imported food products.

3. *What future prospects and opportunities does the technology offer?*

The technology clearly offers not only opportunities for improved economic production, but also the prospect of enhanced disease resistance through either improved natural disease resistance or better means of controlling disease. This would have a beneficial effect on both human and animal welfare.

4. *Which developments in biotechnology raise issues of safety and how should they be addressed?*

The release of genetically modified organisms, whether they be in connection with agriculture or any other industry sector, will be seen as carrying some element of inherent risk. It is necessary, however, to view this risk in the appropriate context with regard to safety to users, workers and environment.

The full assessment of these risks, which industry must accept if the public is to accept such developments, is largely covered by current or pending legislation. However the future development of biotechnology and its continued use as a responsible scientific tool is dependent on the structuring of legislation at the present time and this area should not be overlooked in setting out a long term programme for biotechnoligical controls.

5. *Should biotechnology be regulated by an industry specific regime?*

To ensure that the benefits of biotechnology are efficiently translated to the market place, it would be appropriate for an industry specific regime to be implemented in order that unnecessary costs and delays were minimised. Wherever possible the harnessing of legislation to current industry statutory testing should be encouraged.

6. *From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

The nature of biotechnology and the widespread areas of its application would make horizontal regulation extremely difficult to apply. This can be seen in the current EC directives relating to biotechnology which are being applied in areas for which they were originally unintended and, therefore, unsuited.

Whilst horizontal regulation would not be appropriate, there should be a degree of commonality between the vertical regulations applied in the various industry sectors.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

The most suitable method, as outlined in the previous answer, would be to ensure appropriate vertical regulation at the outset. If this was not achieved then such an evolvement, as outlined, would be a suitable alternative.

8. *How do current regulations compare with those of other competitor countries?*

We do not have sufficient information to put forward an answer to this question.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards*

1. *research*
2. *product development*
3. *investment*
4. *location*
5. *sales and marketing?*

Over-regulation will lead to a reduction in the level of research, product development and investment, putting the UK at a competitive disadvantage. Whilst there is a clear need to satisfy public demand for adequate control, care should be taken to ensure the burden of legislation is no more restrictive than major competitors.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

The present regime is unlikely to prevent exploitation by British industry. However, future regulation must be drawn up bearing in mind the major competing countries if such a situation is to be avoided in the future.

11. *How best can issues of public acceptance be addressed?*

In order that the public are reassured, there must be a completely unbiased release of information with full acknowledgement of both the benefits and risks. Other Associations are exploring methods for bringing about informed debate and this question will, no doubt, be answered more fully by them.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

From an agricultural viewpoint the issue of food labelling requirements is an area where excessive legislation could have a serious knock-on effect.

It is also essential to have industry compliance costs in mind. If these become too high, the UK industry will inevitably become uncompetitive with its competitors in countries less tightly or less bureaucratically regulated. We recognise the role which could be played by international agreements in limiting this effect, which the Committee may also wish to take into account.

Evidence from the United States Embassy

1. *How important does your government perceive biotechnology to be?*

The United States is generally acknowledged to be the world leader in biotechnology, both in basic research and in the commercial development of biotechnology products. This preeminence has been particularly evident in the biomedical sciences, but the statement can also be made for agriculture. Preserving the US lead, and assuring a strong competitive position for the country's biotechnology products, has therefore been a priority objective, and a stated policy goal, of the executive branch of the US government for the last decade.

Through the office of Science and Technology policy (OSTP), the Executive Office of the President has acted to assure that Federal policies for biotechnology research and regulation maintained US competitiveness, while protecting health and the environment.

The current US administration has pledged to "reinvigorate" the OSTP, and to use and strengthen the Federal Coordinating Council on Science, Engineering and Technology (FCCSET) for coordinating the research and development programmes of Federal agencies ("Technology for America's Economic Growth," President William J Clinton and Vice President Albert Gore Junior, 22 February 1993, pp 4 and 9). The existing biotechnology Research Subcommittee (BRS) of the FCCSET, which has overseen the US Biotechnology Research Cross-Cut Initiative, will be continued and supported. The BRS has monitored US expenditures for biotechnology since 1990 through the cross-cut budget initiative, and reports that Federal expenditures for biotechnology research were $3.8 billion in 1992, and will be $4 billion in 1993. Expenditures for basic agricultural research were $200 million in 1992, or five per cent of the total US Federal investment in biotechnology.

2. *Which developments in biotechnology are thought to raise safety issues?*

The safety of laboratory experiments with recombinant DNA molecules has been addressed since 1976 by the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules (DNA Guidelines). The NIH Guidelines were initially based on conjectural hazards and a series of containment levels based on these hazards. The restrictions have been gradually relaxed as information has been gathered to establish the actual safety record for use of the organism(s).

The extensive testing of recombinant DNA-developed organisms and products in the laboratory under the NIH guidelines has generally precluded the existence of safety problems in contained experiments. US Federal agencies have established regulatory programmes governing releases of recombinant-DNA organisms and products, based on the nature of the product and the environment into which it is introduced, that provide oversight designed to protect human health and the environment. Thus, any safety issues associated with releases of the biotechnology products are addressed in the research and development stages.

For example, when transgenic plants are tested in the field, the questions addressed include weediness, transfer of engineered traits to wild relatives, alteration in disease susceptibility or resistance, and impacts on established agricultural practices. These issues are considered on a case-by-case basis during the Federal regulatory review process. To date, no environmental impacts have been identified from the 365 field tests of genetically engineered organisms conducted on 724 sites under permits issued by the US Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS).

3. *In your country, is biotechnology regulated by a specific regulatory regime?*

The US Federal policy for biotechnology, which was published in final form in 1986 as the Co-ordinated Framework, is based on the conclusion that existing US laws "would address regulatory needs adequately" (51 FR 23303, 26 June 1986). The fact that biotechnology could be applied in so many different areas of endeavor also was thought to preclude "an alternative, unitary, statutory approach" (51 FR 23303).

4. *Do regulations distinguish between contained use and general release (for experiment or marketing)?*

As indicated in the previous answer, under US Federal regulatory policy, genetically engineered organisms are regulated under existing authority, on a case-by-case basis according to the end-use of the product. For example, certain genetically engineered plants are regulated by USDA's APHIS in 7 CFR Part 340 under the authority of the Federal Plant Pest Act (FPPA) and Plant Quarantine Act (PQA). The regulations establish a permit requirement for the introduction, which includes importation, interstate movement and release, of certain genetically engineered organisms developed through the use of recombinant DNA techniques. The requirements for a movement permit under containment (7 CFR 340.3(c)) and for a separate permit under containment conditions (CFR 340.3(b)) are separate and distinct, but are addressed in the same set of regulations.

Before an organism subject to the regulations in 7 CFR Part 340 could be developed commercially, it must be granted non-regulated status through a petition procedure. The potential product could also be subject to regulations administered by the Food and Drug Administration under the authority of the Food, Drug and Cosmetic Act, or to regulations administered by the Environmental Protection Agency under the authority of the Federal Insecticide, Fungicide and Rodenticide Act.

5. *Is regulation in your country "horizontal" (where a product is judged through the process by which it is derived) or "vertical" (where a product is judged by its characteristics)? Which is preferred by your government?*

US Federal policy for biotechnology has been based on the premise that the product, rather than the process, should be regulated. This policy position was supported by the findings of the special committee convened by the Council of the National Academy of Sciences, which were published in the 1987 volume, *Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues*. The committee's key findings included the conclusion that an assessment of the risks of introducing recombinant DNA-engineered organisms into the environment should be based on the nature of the organism and the environment into which it will be introduced, not on the method by which it was modified." (page 7)

6. *Is biotechnology publicly accepted in your country?*

The most recent attempt to determine the degree of acceptance of biotechnology was the telephone survey conducted in 1992 by the North Carolina Extension Service. The initial analysis of the survey prepared by Dr Thomas Hoban and Dr Patricia Kendall yielded a number of general conclusions, including the following:

- Most people were positive about the concept of biotechnology.
- There are indications of high expectations concerning the potential for biotechnology to provide benefits.
- Almost two-thirds of all respondents supported the use of biotechnology in agriculture and food production.
- Some apprehension is evident for certain applications of biotechnology, with lower acceptance for biotechnology when used with animals, as compared to plants.

Evidence from Professor Sir David Weatherall FRS, Regius Professor of Medicine, University of Oxford

As promised in my letter of 4 March, because of my inability to attend to give oral evidence on 29 April, I enclose some written comments. I have set them out using at least some of the headings that you have suggested.

1. *My interest in biotechnology*

Because of a long-standing committment to the application of molecular and cell biology to medical research and practice, and because I direct the Institute of Molecular Medicine in Oxford, I have a particular interest in the applications of biotechnology to medicine. This ranges from the science itself to the ethical issues which are raised by the medical applications of biotechnology.

2. *Why is biotechnology important to UK industry?*

From the medical viewpoint biotechnology will play a key role in the British pharmaceutical industry in the future. The scope is enormous, ranging from diagnostics through computer drug design to gene therapy and the development of many active biological mediators of great therapeutic potential.

3. *Future prospects*

It is already clear that the biotechnology industry has major applications throughout medical practice and offers particularly exciting opportunities for tackling some of the intractable problems of western society including heart disease, cancer, major psychiatric disorders, and rheumatism and autoimmunity.

4. *Safety issues*

The medical aspects of biotechnology are particularly complex. They include both issues of safety with respect to recombinant DNA technology and genetic manipulation but also encompass a wide variety of new and novel ethical questions. Each will have to be dealt with independently as it arises. For example, the enormous current interest in gene transfer therapy poses problems both for industry and for the medical profession. Many of these have been dealt with by the Clothier Committee and, hopefully, when the Government finally get round to setting up a central committee to monitor and control applications for gene therapy these complex problems will be sorted out for each individual application. Aspects of safety range from the appropriate way to control the development of recombinant retroviral vectors, with their infectious potential, the side effects of this type of treatment in patients, and a careful risk-benefit analysis for each different condition treated.

5. *Regulation by an industry specific regime*

The medical aspects of biotechnology are complex and cannot be left to industry alone. A great deal of thought will be required in this particular area. For example, when work in research laboratories reaches the stage at which it has clinical application, whether the work stems from industry or academia there will come a time when technology transfer is essential ie when laboratories have to be set up for large batch preparation of biological materials. In the UK this is a major problem because of the lack of venture capital money and industry disinterest in anything that is not already developed to the stage at which it is clear that it has therapeutic potential. The regulation of this "no-mans's land" of biotechnology will have to be thought through very carefully and will probably require control systems to be tailor-made for each individual new area of development. It certainly cannot be left to industry because a great deal of it will have to be undertaken by university or research council laboratories before it gets to the stage of industrial exploitation.

6–7. *Horizontal versus vertical regulation*

The history of recombinant DNA technology suggests that, overall, the "vertical" approach will be much more applicable, certainly in the biomedical field. There will be undoubtedly a phase of evolution, though what you call "horizontal" regulation is, in many areas, already well advanced.

One major problem which, following my experiences on the Clothier Committee I am sure we must address, is the plethora of bodies which feel they have an "interest" in the control of a new clinical development. In the case of gene therapy this includes the Committee on the Safety of Medicines, the various genetic regulatory and safety at work bodies, local ethics committees, the numerous other ethical committees, the Clothier Committee and its successor, and so on. There is a danger that a new development will never get off the ground if biotechnology inventions come under the scrutiny of too many controlling bodies. This is a particular problem in the biomedical field.

8. *International comparisons*

Some of the problems being encountered in Germany and other parts of Europe underline the complexities of biotechnology, particularly as related to medicine. In Germany, ethical issues have become a major factor in the biomedical application of biotechnology and I believe that some of the larger companies are moving activities to the USA. Although we are not yet facing problems of this type in the UK and, I believe, have handled such sensitive issues such as embryo manipulation and gene therapy quite well so far, this will be a continuous danger to this field.

The major centres for biotechnology in Southeast Asia are Singapore, Thailand and, I suspect, Korea. I think the situation in Singapore is similar to the UK but don't know a great deal about regulation in Thailand or Korea.

9. *The likely consequences of the regulatory regime on competitiveness*

I don't think there is a problem here provided that we combine defining what we require for safety with a proper public relations exercise on the more ethical and pastoral issues raised by biotechnology.

If we are not to go the same way as Germany, with the danger of reducing the opportunities for biotechnology in the UK, we will have to continue to work very hard in the area of public appreciation of science. This year I am President of the British Association for the Advancement of Science and I have been very depressed and disillusioned about the amount of government support for the work of the BA and similar bodies. The kind of issues that you are considering are being aired as as broadly as possible, particularly at this year's Annual Meeting at Keele. Yet the response from government and industry has been miserable, with the notable exception of one company. I don't think that the British biotechnology industry is sufficiently aware of the importance of taking the public along with them. Nor do I think government is aware of the importance of the public appreciation of biotechnology and its implications.

In summary, I list the following problems as those needing fairly early consideration:

(a) Regulation should be developed in a "vertical" type of organisation which deals with specifics. In the biomedical field the work of the Clothier Committee and the body which (hopefully) will be set up shortly to monitor the use of recombinant DNA technology for human gene transfer for therapy of many different diseases is is a good example of the way that we should move. One or two expert monitoring groups set up along these lines would cover most of the medical developments in biotechnology. This type of problem illustrates well the complex interactions that will be required between research in academia, the pharmaceutical industry, and the purchasers and providers of health care. I would see a number of "vertical" developments of this type, perhaps looked after by the body which deals with the more "horizontally" related problems in the way that GMAG and its successor has done so well.

(b) Regulation must be backed up by a proper dialogue between industry, academia, and the public as to what is acceptable in biotechnology. We have the mechanisms for developing the public appreciation of science in the UK but they are grossly under-supported.

(c) If we are to make the best use of what biotechnology has to offer we must not let the erosion of the funding of science continue. The biotechnology industry requires a constant input of bright, well-trained scientists and this, in turn, requires that the funding for science in the universities must be improved.

(d) There is a major problem in the UK with technology transfer and its control. Venture capital money is limited and there is considerable difficulty in transferring the bright idea from the basic research laboratory to industry. The bright young men in my Institute are inundated with people from the USA who want to help them develop their inventions; this is not happening in the case of British industry and there is a major gap between the basic research laboratory and the biotechnology industry as a whole. I believe this a much greater potential problem than the development of a system of regulation which makes us less competitive in the world market; but the problems in Germany should be a constant reminder of how hard we will have to work to maintain public awareness and acceptability.

Evidence from The Wellcome Foundation Ltd (Prof T M Jones)

1. *What is your interest in biotechnology?*

The Wellcome Foundation has been a pioneer in the UK biotechnology industry and has experienced continued growth in its biotechnology endeavours. Wellcome has modern, comprehensive research, development and production facilities in the UK at its Beckenham site and large production facilities in Spain and in Rhode Island USA.

Biotechnology encompasses an immensely powerful set of methodologies for biomedical research which find an essential and ever increasing application in the investigation of normal and pathological processes in the development of diagnostic tests and in the prevention, treatment and cure of disease.

Secondly, and importantly, the methodologies constitute an enabling technology for the development and manufacture of traditional and particularly small molecular weight biochemicals and pharmaceutical compounds.

Thirdly, the technology is currently the optimal and, in many cases, the only means available for the development and large scale manufacture of a wide range of novel biopharmaceuticals, including therapeutic proteins and monoclonal antibodies for the treatment of important medical conditions.

For example, currently Wellcome produces two biopharmaceutical products with a sales value of some £40 million, predominantly in export markets. In addition, it has licensed its technology to Japan where one of the products (Sumiferon) is now the second largest product on the Japanese pharmaceutical market.

2. *How and why is biotechnology important to UK industry?*

Biotechnology is important to UK industry because it represents not only a route to novel biological products (eg cytokines, gene therapy, etc) but it is also an essential skill in the prosecution of existing processes of drug discovery. The UK still has an excellent skill base in this area and is one in which we can compete with Germany and Japan. In addition, biotechnology is increasingly significant in a wider range of scientific, technical and commercial applications which should lead to a general improvement of the global quality of life. Although outside the pharmaceutical field, this may include such subjects as: foodstuffs, agriculture, horticulture and energy. Industry and academia in the UK have played a predominent role in research, development and manufacture in a number of these areas and it will be essential to maintain leadership to fully exploit the fruits of the investment made in the UK to date.

3. *What future prospects and opportunities does the technology offer?*

Biotechnology offers prospects for the treatment of disease or the solving of complex chemical processes which cannot be tackled, at present, by conventional chemical/physical technologies. It is important, however, that biotechnology is not seen as applicable only to "niche" activities but as an essential part of the technology of to-day and tomorrow. Too often, biotechnology in the pharmaceutical industry is associated with small, start-up (usually academic based) laboratories who have no "downstream" technology/marketing/commercial facilities. Biotechnology can be seen as a significant feature of major, global pharmaceutical company activities.

Work on the Human Genome project should open increasing avenues of potential for therapeutic intervention either by small molecules (of chemical origin) or by products produced by biotechnology. This is an important area where the UK should make a valid contribution.

4. *What developments in biotechnology raise issues of safety and how should they be addressed?*

As with any new process or procedure, safety issues surrounding biotechnology raise specific requirements. The procedures currently in use have worked very well and strike an excellent balance between over-regulation and justified concerns of the public. There appear to be few significant concerns which have not already been efficiently addressed in an industry which is closely regulated and where the safety of product is of paramount importance. In addition to patient safety, close attention has also been paid to the protection of staff and of the environment. Measures taken to ensure safety include the careful evaluation and elimination or minimisation or risk by the selection and characterisation of organisms, their containment in use and their inactivation prior to any disposal. Safety testing of products includes rigorous sterility and toxicity testing and also the control of residual DNA levels. There is, of course, a need for constant vigilance in the prevention of adventitious contamination, including the reaction to unforeseen emergence of new novel agents and to ensure the quality and safety of starting materials, the consistency of processes and the characterisation of the final product. In this respect, it is noteworthy that modern biotechnology has the capability to eliminate many of the risks associated with classical biological products, for example, the removal of the risk of HIV infection in the treatment of haemophilia by the use of Factor VIII produced by recombinant DNA technology rather than by extraction from human blood.

In some field of biopharmaceutical products (notably horticulture and in pest control) concern has been raised over the release of living genetically modified micro-organisms, insects and plants.

In addition, the genetic modification of animals (whether for experimental purposes or for food production) has raised concern. The subject of gene therapy—using products developed through biotechnology—will be the continuing subject of debate as therapies emerge which can modify disease processes.

It is important that during the development stages of such products, risk assessment is carried out and an objective, informed, public debate stimulated on the key issues. Safety concerns in biotechnology are best addressed by ensuring that R&D and Production is carried out by appropriately trained staff in adequate and suitable premises which are adequately equipped, serviced and monitored in accordance with codes of Good Practice.

Premises and procedures should be licensed and the activities should also be subject to regular independent regulatory inspection. It is noteworthy that these measures are already catered for in the UK through the code of Good Manufacturing Practice and Medicines Regulation.

5. *Should biotechnology be regulated by an industry specific regime?*

It is important to recognise that within pharmaceuticals, biotechnology is a component part of the overall pharmaceutical process and should not be regarded as a distinct and separate entity requiring separate regulation.

6. *From a technical point of view, is horizontal regualtion (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?*

In the specific example of biological agents produced through biotechnology processes horizontal regulation is probably the best solution since the process needs to be thoroughly examined to ensure that any foreseen problems are properly addressed. Such horizontal regulation is appropriate during the *development* stages of a biopharmaceutical product.

However, once the characteristics of the process and the product have been investigated and consistency established, vertical regulation should be more appropriate.

In practice, a combination of process and product regulation is currently applied in the UK. Regulatory legislation should allow for both approaches in the initial phases of development with the emphasis shifting wholly or partially from horizontal to vertical legislation according to accumulated knowledge and experience. The European "high tech" regulatory consultation procedure is already established as a somewhat separate review process to conventional pharmaceutical products. This is already a laborious and complex procedure to follow which can result in delays to product entry to Member States and consequential loss of therapeutic and commercial benefit. Too many different agencies operating in a separate control would lend complexity to an already difficult situation.

7. *Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?*

Regulation should evolve from horizontal to vertical approach on the basis of accumulating confidence in the reproducibility of the process and the consistency of the product.

This approach is particularly relevant to biopharmaceutical products where the products of the biotechnology are themselves inanimate and particularly accessible to charterisation, eg for a therapeutic protein.

Different considerations apply in the case of the release of live genetically manipulated organisms.

8. *How do current regulations compare with those of other countries?*

(a) ***Europe***

Current UK regulations for biotechnology are subject to harmonisation in accordance with the Laws of the European Community. In theory, at least, all Member States are, therefore, subject to common EC Directives covering many aspects of biotechnology. In practice, the EC Directives are enacted in Member States on different timescales. It is difficult to know whether a level playing field is in operation—although there are suggestions that varying interpretations and levels of enforcement obtain in different Member States. An example would be Germany where Federal Law is administered by 50 separate regional authorities and there has been a lack of discrimination between the risk levels ascribed to different activities. This has resulted in long term delays, high compliance costs and cumbersome documentation obligations, even for establishments and experiments involving genetic manipulation where risk was in a very low category or entirely absent. As a result, there has to date been only one deliberate release of a genetically manipulated plant in Germany as compared with hundreds of releases worldwide.

(b) ***Far East***

In Japan, the emphasis is on more vertical legislation relating to the characterisation of the final product.

There are reports of large scale field trials of genetically engineered plants in the Republic of China which appear to have progressed at a significantly faster rate than similar trials elsewhere. This may imply that regulation and control may be less stringent.

(c) ***USA***

Regulation of biotechnology in the USA contains both horizontal and vertical elements. The 1993 US Biotechnology Research Initiative recognises the need for closer integration between the various Government Agencies, including the US Department of Agriculture, the Food and Drugs Administration and the Department of Health and Human Services and the Environmental Protection Agency. The rapidly increasing number of permits issued for the testing of genetically engineered plants in field trials may well indicate a more efficient and, perhaps, less restrictive regulatory climate than existed formerly in the USA.

Extra Federal funding has been allocated in the 1993 US budget for the further development of regulatory review processes.

9. *What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards:*

1. **Research**

It is clear that any increase in the regulatory bureaucracy will put the UK at a significant disadvantage. We already see job applicants from Germany who specifically come to work in the UK due to problems in biotechnology within their own industry. A similar "brain drain" could easily be caused by inappropriate legislation in the UK. There is a further danger that the pace of research could be slowed unless Government Departments are able to process notifications and consents for biotechnology projects in an expeditious manner.

2. **Product Development**

The regulatory organisations must be resourced to avoid delays in the processing of applications for product licences.

3. **General**

If the UK regulatory climate becomes relatively unfavourable then the most able British scientists and technicians might well emigrate to more fertile pastures while companies would opt for direct research, development and investment in manufacturing facilities in countries other than the UK. This latter is particularly relevant to companies already having global opportunities based in other countries where tax benefits, combined with an adequate science base, can be an attractive alternative to the UK.

The consequence of excessive or restrictive regulation would mean that the UK capability in biotechnology would be increasingly eroded, scientific and technical leadership lost and the competitive position progressively weakened.

In addition, inward investment for biotechnology could also be adversely affected.

10. *Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?*

It is important that conditions for research and development in the UK remain competitive with those elsewhere in Europe and, especially, with the USA. It will be particularly important to monitor the effect of regulation in the UK; particular attention should be focused on the interval elapsing between notification and consent.

Consideration should be given to the design of simple forms to cover multiple activities where possible so that duplication of paperwork, etc is minimised. Thus, for example, the same risk assessment document should serve for various government departments for the purpose of registering establishments, applying for consent for projects, for manufacturing licences and product licences.

Developments in regulatory control outside the UK should be closely monitored to ensure the UK is not disadvantaged and efforts made to maintain a level playing field. The objective of regulatory harmonisation should continue to be pursued within the European Community and extended to other areas.

A long term plan for communication with the public of the basic information about the industry—including its biotechnology component—would be helpful.

11. *How best can issues of public acceptance be addressed?*

Modern, as distinct from traditional, biotechnology has raised safety concerns in some sectors of the general public where it is perceived as unnatural interference, inherently dangerous and likely to result in the release of unknown and uncontrollable life forms. In 1985, for example, a survey of British public attitudes towards novel foodstuffs produced via biotechnology revealed that 70 per cent considered genetic enginerering to be "morally wrong".

62 per cent thought it "unnatural" and 27 per cent thought it "frightening". There is a suggestion that naivete and arrogance in the scientific community may have contributed to these perceptions. Concepts in biotechnology are not readily accessible to the lay person and lack of knowledge and understanding has, on occasions, been compounded by alarmist and biased reporting by areas of the media.

The public perception of risk varies with the area of biotechnology involved. Overall, 50 per cent of 12,800 European respondents believed in 1992 that biotechnology would improve their lives, while 11 per cent believed that it would make them worse. 89 per cent considered that biotechnology should be encouraged for the development of drugs and vaccines as compared with 58 per cent for food technology and 42 per cent for farm animal technology (CUBE Eurobarometer Survey 1992). In the same survey, the responses placed the UK fourth within the 12 EC Member States in terms of awareness of the applications of biotechnology, fourth in terms of acceptance of the potential benefits and the continuation of R&D and tenth in the perception that such work carries risks.

More recent developments in biotechnology have raised new areas of concern, not only of safety but also of ethics, morality and legality. These relate particularly to human life and identity, to socio-economic consequences of biotechnology, to the protection of the environment, to consumer protection, to the rights of animals and to the maintenance of biodiversity. Specific issues include the creation and patenting of new life forms (for example the transgenic Harvard "Oncomouse"), the patenting of human genomic sequences, the expanding area of gene therapy including the correction of genetic defects and the controversial, and as yet, theoretical application of germ cell gene therapy.

Public acceptance of biotechnology is best fostered by education—especially at school level—and the promotion of its beneficial effects. Confidence will be increased by applying the principle of transparency—as far as is commensurate with the protection of intellectual property and commercial confidentiality. The agencies involved include schools and universities, government departments and trade associations, including the ABPI, BIA and CBI, the British Association of the Advancement of Science and all media channels.

Good material is already available from several of these sources in Britain and elsewhere but continuing attention is needed to ensure that the information is presented in forms tailored to different audiences and widely disseminated.

12. *What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?*

Other important factors in promoting competitiveness include the following:

- the protection of intellectual property and of international patent rights. Within the EC there is a lack of uniformity of patent law in the biotechnology field resulting in uncertainty as to the strength and value of biotech patent rights. In Japan and the USA where the biotechnology industry is more competitive, a more favourable patent environment exists for biotech invention. The discrepancy between the position in the EC and that in Japan and the USA has been recognised by the European Commission through a draft Biotechnology Directive which would have gone some way to putting the EC biotech industry on the same footing as that in the US and Japan. Unfortunately, it has been hijacked by a number of groups pursuing vested interests particularly those claiming to represent the interest of farmers, plant breeders and animal rights. As a result, the original objective of the

Directive has long been lost. It is preferable that the draft Directive be not enacted at all rather than enacted in its present form.

- the provision of government incentives for the development of the industry through grants and tax advantages.
- the close integration of relevant government agencies and continuing dialogue and consultation between government, academia and industry.
- the further development of international harmonisation in regulatory affairs and in patent protection.
- the vital maintenance and improvement of the premier UK scientific base, including education and training in schools, universities, research institutions and government laboratories by the provision of appropriate funding.

If I can be of any further assistance please do not hesitate to contact me.

Letter to the Clerk from Professor Mark Williamson, Department of Biology, University of York

Thank you for letter of 26 February asking me to submit written evidence on the questions you enclosed.

1. *My interest in biotechnology*. By "biotechnology", I presume the sub-committee has in mind advanced modern technology, particularly those techniques that involve the manipulation of DNA. I am a population biologist, and my only direct concern with biotechnology is on environmental releases of novel organisms derived by such biotechnological processes. I am a member of the Advisory Committee on Releases to the Environment, and have been a member of all its predecessors since 1986. I have also advised both the CEC and the OECD in these matters.

2. *Importance of biotechnology to UK industry*. In the environmental use of biotechnology, there is a prospect of development of novel organisms and that will be important in agriculture. There is also the possibility of other environmentally useful developments. With our national skills in basic biotechnology, it should be possible for UK industry to be competitive, innovative and profitable. Most products intended to be used in the environment should have international sales.

3. *Future prospects and opportunities*. There are many areas in which biotechnology offers the possibility of environmental remediation. At the moment, the most likely prospect is products that decrease the need for chemical pesticides. It is particularly unfortunate the industry has gone for herbicide resitant plants at one of its main lines of development, as these inevitably require the use of herbicide, There are arguments about whether this will mean more or less herbicide, but the fact that herbicide will have to be used is incontrovertible. What environmental biologists would like to see in this field is the development of products that lead to the decreased use, or even the cessation of use, of harmful chemicals of all sorts.

4. *Issues of safety*. The vast majority of biotechnological developments that are known about at the moment will have no new safety implications in the environment. However, there is a small possibility of a major environmental effect. More immediately, several of the products being developed could well have undesirable side effects. For instance, the promotion of herbicide resistant sugar beet is likely to exacerbate the weed beet problem. Weed beet is a form of beet which is a result of bad agricultural practices, and a clear example that agriculture does do harm to the environment on occasion, Similarly, plants that contain insecticide, particularly the *Bacillus thuringiensis* toxin, will give rise to toxin resistant insect strains, That will be unfortunate, though the environmental damage will be small. Viruses improved by biotechnology to have great killing power against known pests may incidentally, if proper precautions are not taken also have great killing power against desirable insects. The major issue for me in this field is that these developments are in some cases foreseeable, yet there seems to be no mechanism whereby the desirability can be discussed, let alone agreed, at an international level. Agreement at a national level would be readily bypassed merely be taking the product to a different country.

5. *An industry specific regime?* My views on this will become clear from my answers to questions 6 and 7.

6. *Horizontal or vertical regulation?* It is widely agreed amongst scientists that it is the product not the process that has to be assessed in discussing the likely environmental damage. That would point to vertical regulation, However, the reason why some products may be dangerous is a result of their novelty, and their novelty arises from the process by which they are formed. The speed of evolution, and the ability of agricultural scientists to create improvements is limited by the genes that are available. What biotechnology offers in this area is the prospect of bringing genes from distantly related organisms, say from bacteria to plants, so that genuinely new novelty is available. So although it is a product that should be regulated, it is necessary to have horizontal regulation to decide which products need regulation.

7. *Evolution of regulation*. It would follow from my arguments on point 6, that this would be desirable and sensible once sufficient experience has been had of various novel products.

8. *Comparable regulations*. British regulations are in effect the European regulations, and are determined for the moment by directive 90/220. The interpretation of this directive may differ in different countries. As a generalisation, the more northern countries, such as Denmark and Germany, tend to take a stricter view of

what is required than some more southern ones. It may well be related to the level of public concern in those countries, which I will return to under point 11.

I have no knowledge of regulations in the Far East.

In the USA, the regulatory system can only be described as chaotic. A decision was taken early on not to introduce any new legislation, but to adapt the old legislation. This is insufficient, and has led to public concern, which again I will attend to under point 11. It seems to me that the Americans have managed to achieve the worst of most possible worlds from an environmental point of view. They have raised public concern where it need not be raised; they have not instituted regulatory systems which would allow the industry to develop internationally and with consumer confidence.

9. *Regulatory regime and competitiveness of UK industry.* In Europe, as we are part of Europe, there should be no differential effects on the UK industry. The regulatory laxness in the USA might tempt some companies to move some aspects of their work to the USA. More seriously, there will be non-OECD countries without regulation, and some industries will certainly be tempted to move some parts of these five operations outside OECD countries.

10. *Regulation and exploitation.* There is no reason at all why the present regulatory regime would prevent the exploitation of research conducted in the UK. But conforming to regulations is an expensive process. Consequently there may well be temptation to work outside the OECD, which would possibly make the UK science base less relevant to the work conducted.

11. *Public acceptance.* The British committees I have sat on have almost invariably taken the view that the function of regulation is two-fold. The first is to ensure that environmentally harmful products are not released. The second is to assure the public that there is sufficient expert examination of what is being proposed that they can concentrate on other environmental issues. The second point is perhaps optimistic. Nevertheless, the story so far of the Flavr Savr tomato in the US shows what happens when there is not such a public reassurance. It seems to me to be a highly desirable commercial product, giving the consumer a better tomato to eat. I can see no environmental risk from its development. Nevertheless, because of public concern, the Campbells soup company has, for the moment at least, decided to cease development of it. Its announcement said it "has no plans to market any genetically engineered food in the foreseeable future". The failure to communicate properly with the public is far more likely than any regulatory process to inhibit the industry's development. The attitude of the American Food and Drug Administration is particularly deplorable in this context.

12. *Other factors.* A major gap, as I see it, in the system that we have at the moment is that the absence of any mechanism whereby the eventual consequences of a product can be discussed in its early stages. Small scale trials are almost invariably totally safe, but they may be so safe as to give no information about eventual environmental hazards.

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